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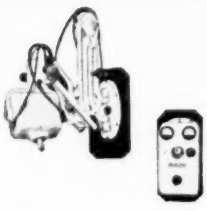

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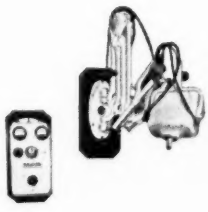

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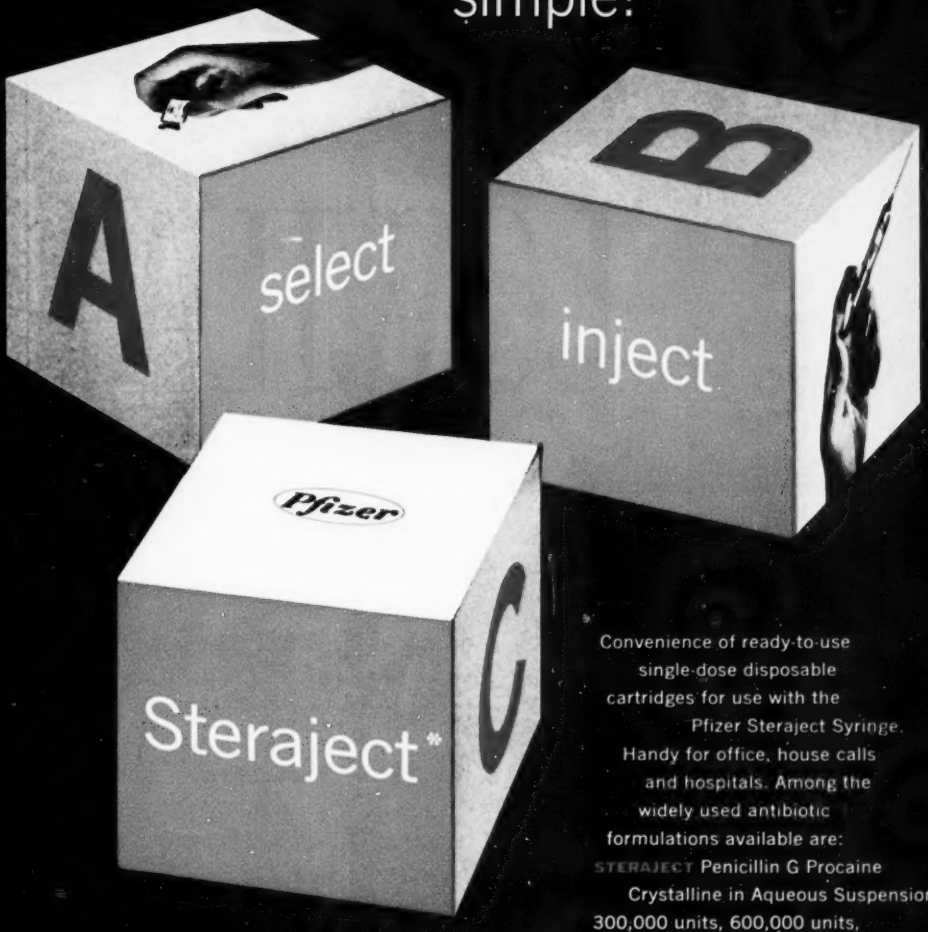

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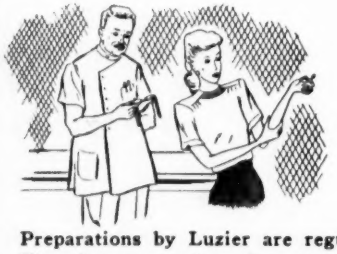

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FACTS ABOUT *Synthetic*

In the short space of five years synthetic detergents have made a tremendous change in the household washing habits of American housewives. At the start of 1948 they accounted for less than 10% of the "laundry soap" business; by the end of 1952 they accounted for over 70%. The product enjoying the greatest popularity in this classification (Tide) is currently being used by one woman out of every four who do their own dishes, and one out of every three who do their own laundry.

For your information the Chemical Division of The Procter & Gamble Company has prepared this article, discussing some of the differences between synthetics and soaps which formerly were widely used for household washing.

How synthetic detergents differ from soaps

Synthetic detergents are organic compounds with molecules whose opposite ends are highly polarized like those of soap; one end consists of the type of structure which is oil soluble, the other consists of the type which is water soluble.

Magnesium and calcium soaps formed by interaction of sodium soaps with water hardness are among the most insoluble of compounds. The precipitation which occurs with soap in hard water wastes soap and causes cloudy glassware and unsightly deposits. The "tailor-made" molecules of synthetics do not form these insoluble compounds in hard water. They, therefore, leave surfaces cleaner because they are free of any precipitated "soap film" formed during rinsing. Also, unlike soaps, in solution, synthetics can be used at almost any pH. Soaps, of course, must be kept at pH 10 or above, or they will split into fatty acids. Most synthetic products in general use have solution pHs from 6.0—10.0. Few are above the pH of soap.

The special washing abilities of synthetic detergents

As a consequence of the characteristics discussed above, synthetics are particularly well-suited for washing off acidic soils which would destroy soap. Since they aren't destroyed by hardness or by salts of other metals as soaps are, they are well-suited to washing a great variety of things which could be washed only with alkalis before—for instance, glass laboratory utensils.

The effect of synthetic detergents on bacteria

The synthetics in general and widespread use have about the same general effect on bacteria as soaps —that is, they have some germicidal effect on some strains, but for creating relatively sterile conditions, synthetic detergents rely more on removing bacteria than on killing them.

Detergents

The effect of synthetic detergents on skin

Over the past seven years Procter & Gamble has included these synthetic detergents in the continuing series of tests, designed to measure the effect of washing products on skin. In addition to the routine patch and arm-immersion tests, Procter & Gamble has conducted, under careful medical supervision, extensive clinical and home-usage tests of all its products, including the new synthetic detergents. These tests indicate that household detergents in use today, as a class, do not differ greatly in their effect on the skin from the general-purpose package soaps which have been used for years. Some have a lower pH than soaps and, hence, less effect on persons sensitive to alkali.

Like soaps, the detergents generally are mild primary irritants, but a fact not generally realized is that on the average person subjected to patch tests or immersion tests, most detergent solutions cause less skin reaction than do soap solutions.

Women have had many years in which to learn whether or not all soaps or certain soaps prove irritating in each particular case. Any problems arising from the effect of soap on skin have, therefore, been spread over decades. In the case of washday detergents, practically every woman in America was exposed to these products in a concentrated period of two or three years.

This great popularity and widespread use of synthetic detergents, together with their relative newness on the market, have resulted in a situation where synthetic detergents are likely to be suspected as the cause of many cases of dermatitis where they probably are not involved at all. With almost all housewives now using synthetic detergents for one or more purposes in their homes, it is inevitable that when a physician sees a case of hand dermatitis, a history of exposure to detergents will be obtainable. The significance of the dermatitis must be appraised against the background of the wide use of the detergent products.

For further information . . .

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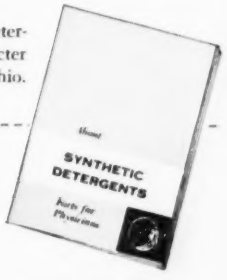

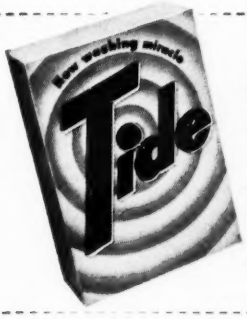

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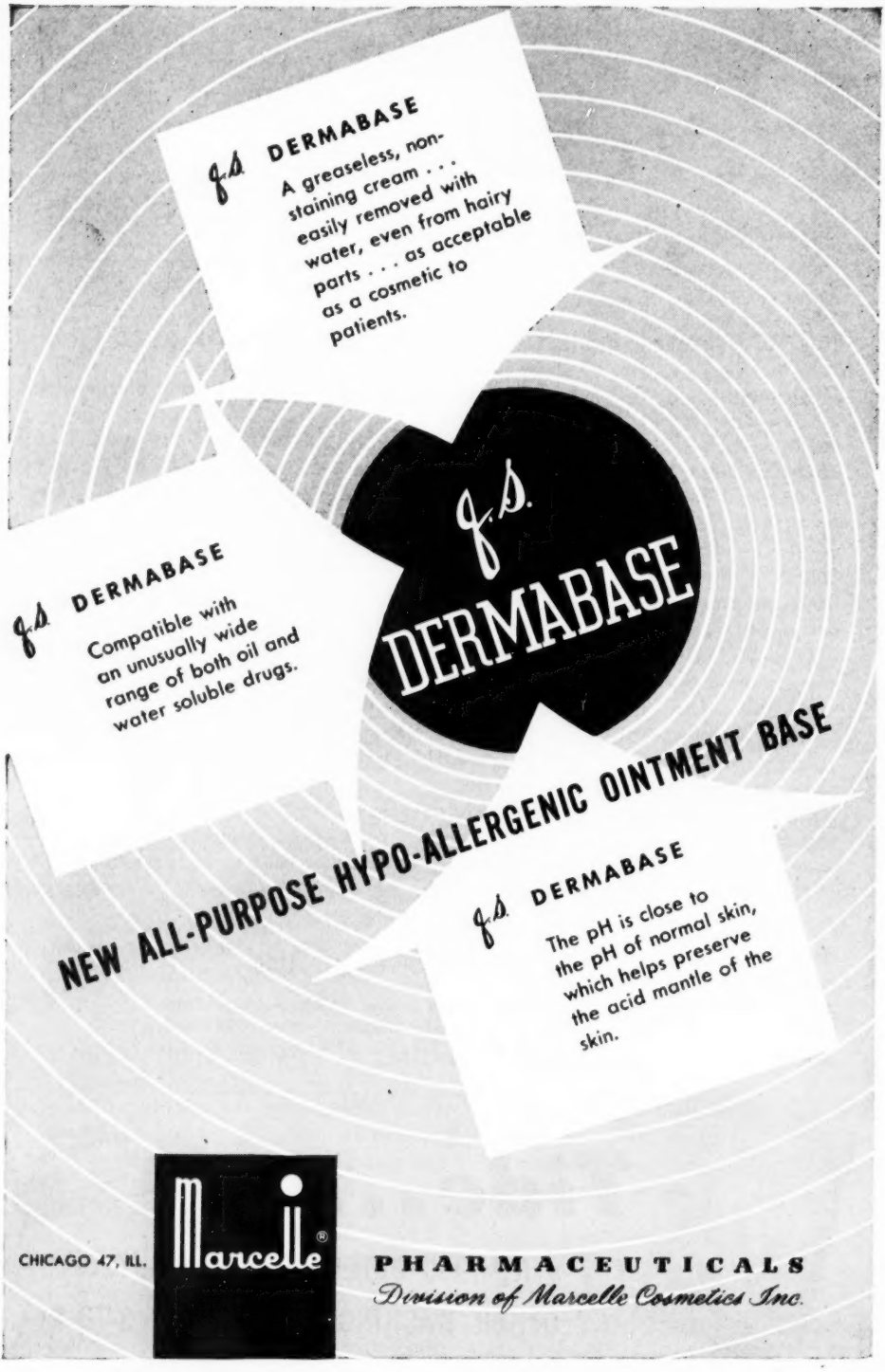
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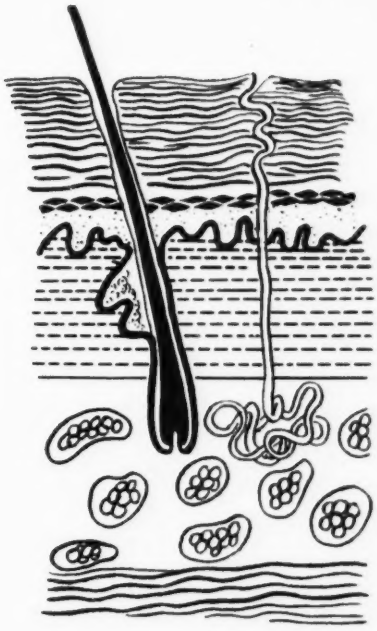

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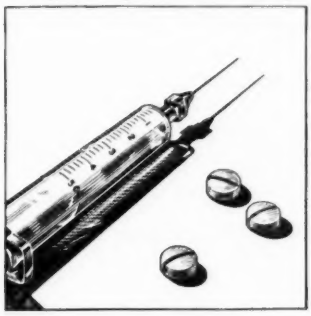

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BACILLUS ANTHRACIS

Observations on In Vitro Sensitivity to Seven Antibiotics with a Comment on Therapeutic Implications

WILLIAM P. BOGER, M.D.
NORRISTOWN, PA.

ANTHRAX, while not a rare disease, is an uncommon one, and only an occasional investigator has the opportunity of receiving within a short span of time a significant number of strains of Bacillus anthracis freshly isolated from human cases of anthrax. This, plus the fact that there is a general reluctance to handle the organism, based on the difficulty of destroying anthrax spores which have once contaminated a room, seemed to justify the reporting of the present study.

Because of unique circumstances, 29 strains of B. anthracis isolated from patients suffering from cutaneous anthrax became available to us. Fifteen of the strains had been preserved at 20 C. for periods ranging from 10 to 13 years after their isolation from human infections.[1] The virulence of these strains was established by guinea pig tests, with deaths occurring in 100% of the animals within 96 hours and in the majority of cases within 48 hours.[2] The remaining 14 strains were freshly isolated from human cases of the disease.

METHODS

Solutions of aureomycin, chloramphenicol, neomycin, penicillin, polymyxin, streptomycin, and oxytetracycline (Terramycin) were prepared as follows: chloramphenicol and streptomycin, 500 γ per milliliter; aureomycin, neomycin, polymyxin, and oxytetracycline, 100 γ per milliliter, and penicillin, 66 γ per milliliter (100 units per milliliter). Further dilutions of these standard solutions were made in buffered saline in order that the addition of 5 cc. to 15 ml. of culture medium would result in the final dilutions of antibiotics tested; thus each Petri dish contained 20 ml. of blood agar in which was incorporated a known concentration of the antibiotic under test. The dilutions of antibiotic tested were as follows: streptomycin, chloramphenicol, and neomycin, 0.8 to 50 γ per milliliter; polymyxin, 0.8 to 25 γ per milliliter, aureomycin and terramycin, from 0.1 to 5 γ per milliliter, and penicillin from 0.06 to 3.2 γ per milliliter (0.1 to 5 units per milliliter). The limit of these ranges of concentrations of the respective antibiotics were set arbitrarily, but the upper limit was regarded as exceeding the plasma concentration of the antibiotic under test that can be reasonably attained when the respective antibiotics are administered therapeutically.

All plates were incubated at 28 C. and read at the end of 24 hours (readings at the end of 48 hours did not alter the results). Under these conditions it was possible to read partial as well

Associate in Medicine, University of Pennsylvania School of Medicine, and Director of Research Therapeutics, Norristown State Hospital.

1. These 29 strains of anthrax were originally isolated from human cases of cutaneous anthrax by Dr. Herman Gold, of Chester, Penn.

2. L. C. Manning, Research Division, Sharp & Dohme, Inc., performed the virulence tests.

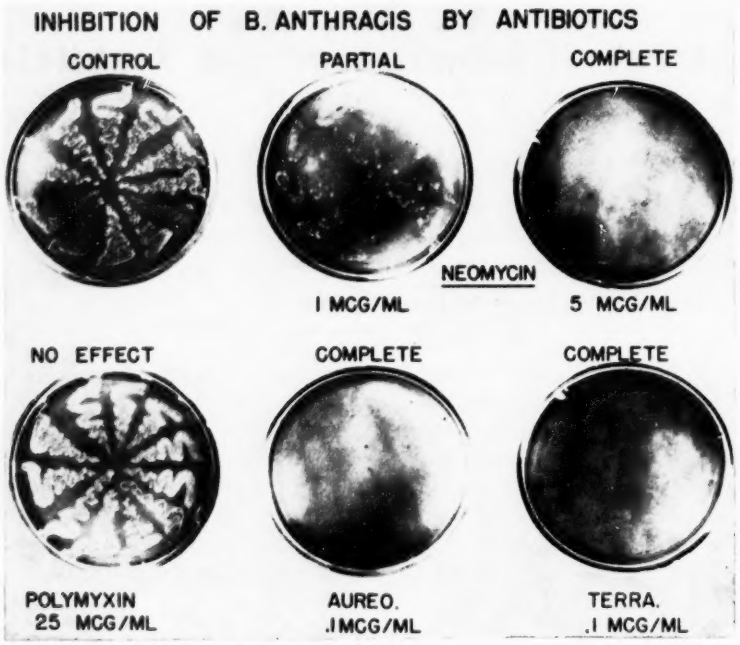

Fig. 1.—Control plate shows the luxuriant growth of 11 strains of B. anthracis. Partial inhibition by 1 γ per milliliter of neomycin as compared with complete inhibition by 5 γ per milliliter of neomycin and 0.1 γ per milliliter of aureomycin and oxytetracycline is shown. Complete lack of effects of 25 mg. of polymyxin is shown by the similarity of this one plate to the control plate.

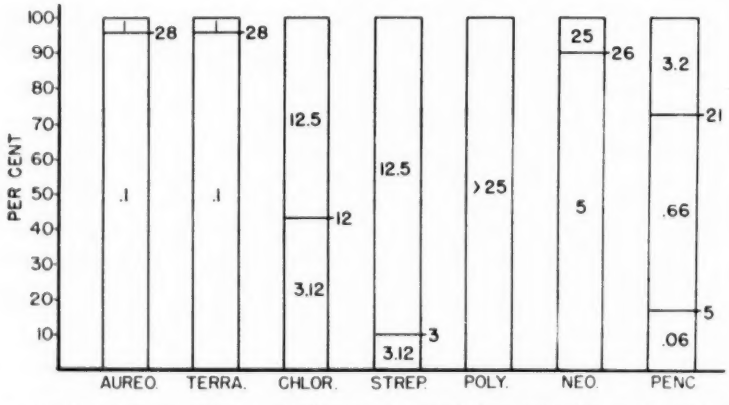

Fig. 2.—Each bar represents the influence of a particular antibiotic on 29 strains of B. anthracis. Numbers in the bars indicate concentrations of the particular antibiotics in terms of micrograms per milliliter. Numbers at the right of the lines dividing the bars refer to the number of strains inhibited by the antibiotic concentration given below the line and within the bar.

as complete inhibition of bacterial growth, but for the purposes of this study all results were reported in terms of complete inhibition. Reference to Figure 1 will indicate the clarity of the end-points reported.

It should be stated that the plate method of determining the in vitro sensitivities here described has been found to give results which indicate in the main that the amount of an antibiotic required to inhibit growth of the organism is about twice that required to inhibit its growth in a liquid medium. Antibiotic treatment of patients based upon plate sensitivity data will therefore be in the direction of overtreatment rather than undertreatment.

RESULTS

Our results are presented in Figure 2. Each bar represents an antibiotic studied. The numerals within each bar refer to the concentration of the antibiotic; the number at the right of the line dividing each bar represents the number of strains inhibited by the antibiotic in the concentration given in the bar below the line. The cumulative percentage of strains inhibited by a particular concentration can be determined from the scale at the left of the charts; for example, 0.1 γ per milliliter of aureomycin inhibited 28 strains and 1 γ per milliliter inhibited 29 (100%) strains. As stated previously, all results here reported are based on complete inhibition of bacterial growth as determined macroscopically at the end of 24 hours' incubation at 28 C.

COMMENT

The similarity in behavior of anthrax bacilli toward aureomycin and oxytetracycline is striking. With the exception of one of the 29 strains they may be said to have behaved uniformly with respect to these two agents. All the strains proved resistant to polymyxin. This "polymyxin resistance" has been observed by others.[3] The greatest variability among the strains was observed with respect to penicillin, an interesting observation, since the group of strains yielded in a more or less equal measure to aureomycin, oxytetracycline, and polymyxin. Although the values reported would seem to indicate a difference between streptomycin and neomycin, it is doubtful whether the susceptibility of these 29 strains to these two agents is significantly different. The assignment of therapeutic significance to the absolute concentrations of the antibiotic agents that are presented in Figure 2 is not warranted, since even if in vitro testing correlates well with measurement of the antibacterial action of antibiotics in the plasma of patients, it is not known (*a*) to what extent the concentrations of antibiotics here tested can be assured at the sites of anthrax infections, or (*b*) whether patients can receive without prohibitive manifestations of toxicity amounts of streptomycin and neomycin that will give plasma concentrations 5 and 10 times their in vitro sensitivities.

In vitro sensitivity tests are carried out in the hope that the results will be helpful in selecting an antibiotic for use in the treatment of a particular infection. To what extent in vitro sensitivity tests can be relied upon for guidance can be called into question, but such data are a reasonably accurate guide when (*a*) consideration is given to the limitation of in vitro sensitivity testing, (*b*) the therapy is directed toward the attainment of plasma concentrations 5 and 10 times in excess of the in vitro sensitivity of an infecting strain, and (*c*) the attainment of this

3. Ruiz Sanchez, F.; Ponce de Leon, E.; Villegas, P., and Novelo, A. M., Jr.: Aureomycin in the Treatment of Anthrax, Medicine, México **29**:211-215 (June 10) 1949.

objective is checked by measurements of the plasma concentration of the antibiotic being employed.

With such concepts of therapy, based on the laboratory findings, it is of interest to examine the results here reported. The identical susceptibility of these 29 strains of B. anthracis to aureomycin and oxytetracycline in our in vitro tests parallels the reported clinical success with these two agents.[4] Plasma concentrations of 1 γ per milliliter, and indeed of 5 and 10 γ per milliliter, are accomplished by the administration of as little as 2 gm. per day of either aureomycin or oxytetracycline. The efficacy of this daily dose in the treatment of cutaneous anthrax has been demonstrated.[4b] Chloramphenicol in concentrations of 12.5 γ per milliliter completely inhibits all the strains tested. While this concentration is numerically greater than the inhibitory concentrations of either aureomycin or oxytetracycline, it is just as readily attained and exceeded by the administration of a dose of 2 to 4 gm. per day of the drug, as are the plasma concentrations of aureomycin and oxytetracycline referred to. Hence, one might predict that chloramphenicol would be an effective agent in cutaneous anthrax, and this has been proved to be the case.[4b]

The use of penicillin in the treatment of cutaneous anthrax was based on the finding that a strain of B. anthracis was inhibited in vitro by 1:100,000 dilution of the antibiotic.[5] Penicillin has been reported to be effective in the treatment of cutaneous anthrax when administered intramuscularly in a daily dose of 100,000 to 500,000 units.[6] The results of in vitro sensitivity tests with penicillin are shown in Figure 2 in terms of micrograms per milliliter of penicillin and also in the more familiar terms of units per milliliter. The results indicate that 5 strains of B. anthracis are inhibited by 0.1 unit per milliliter, 21 strains by 1 unit per milliliter, and 29 strains by 5 units per milliliter. Assuming the correctness of the aim to achieve plasma concentrations 5 to 10 times that of the in vitro sensitivity of an infecting organism, it is of interest to note that 300,000 units of penicillin administered intramuscularly as a single dose does not give a penicillin blood level in excess of 5 units per milliliter for more than a few minutes at best, and that if 100,000 or 300,000 units are administered intramuscularly in divided doses over a 24-hour period, it is doubtful whether plasma concentrations in excess of one unit per milliliter are attained for more than a few minutes during the 24-hour period. Nevertheless, dosages of 100,000 to 300,000 units of intramuscular penicillin administered over a 24-hour period have been reported to be effective in the treatment of anthrax.[6b-d] One might assume that the in vitro testing (at 28 C.) as performed in this study gives results indicative of greater resistance to the

4. (*a*) Ruiz Sanchez; Ponce de Leon, E.; Villegas, P., and Novelo, A. M., Jr.[3] (*b*) Gold, H., and Boger, W. P.: Newer Antibiotics in the Treatment of Anthrax, New England J. Med. **244**:391-394 (March 15) 1951.

5. Abraham, O. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**:177-188 (August 16) 1941.

6. (*a*) Murphy, F. D.; LaBoccetta, A. C., and Lockwood, J. S.: Treatment of Human Anthrax with Penicillin: Report of 3 Cases, J. A. M. A. **126**:948-950 (December 9) 1944. (*b*) LaBoccetta, A. C.: Anthrax: 36 Human Cases of the External Type Treated Successfully with Penicillin, Am. J. M. Sc. **216**:407-410 (October) 1948. (*c*) Ellingson, H. V.; Kadull, P. J.; Bookwalter, H. L., and Howe, C.: Cutaneous Anthrax, J. A. M. A. **131**:1105-1108 (August 3) 1946. (*d*) Holgate, J. A., and Holman, R. A.: Diagnosis and Treatment of Cutaneous Anthrax, Brit. M. J. **2**:575-579 (September 10) 1949.

influence of penicillin than is actually the case in clinical practice (temperature of patients is 99.5 F. or higher), or that the strains producing the infections successfully treated were more sensitive than those tested in this study. It is highly desirable in subsequent studies that the clinical results be correlated with penicillin plasma concentrations.

Streptomycin and neomycin behave similarly in many respects and when administered intramuscularly in the same doses give comparable plasma concentrations. Daily doses of 1 and 2 gm. of streptomycin give plasma concentrations in excess of 12.5 γ per milliliter for a considerable portion of a 24-hour period, and the same is true of neomycin. It might be anticipated that both streptomycin and neomycin would be efficacious in the treatment of anthrax infections, but no reports of the use of either of these two agents in the treatment of human anthrax have come to our attention.

It is of interest that in animal protection studies streptomycin has been shown to be more effective than penicillin against anthrax infections[7] and that in the hands of some investigators anthrax bacilli have been found to be more sensitive to streptomycin than to penicillin.[3] Polymyxin is extremely nephrotoxic when administered parenterally, and on the basis of the demonstrated resistance of all 29 strains to a concentration of 25 γ per milliliter it is problematical whether this agent would be suitable for the treatment of anthrax.

Within the limits of the reported clinical experiences on treatment of cutaneous anthrax, the predictions that one might make on the basis of the study here reported are confirmed. With regard to penicillin, one might have predicated less success in therapy than has been reported. The possibility of treating cutaneous anthrax with streptomycin and neomycin can be entertained, but, since the toxicity of both these agents is greater than that of other agents already shown to be effective, their use is scarcely justified.

CONCLUSION

Twenty-nine strains of B. anthracis have been tested in vitro for susceptibility to seven antibiotics: aureomycin, chloramphenicol, neomycin, penicillin, polymyxin, streptomycin, and oxytetracycline. Uniform sensitivity of all strains to aureomycin and oxytetracycline (Terramycin) was observed; on the other hand, all were resistant to polymyxin. The greatest variation in sensitivity within these strains was observed with reference to penicillin. The degree of sensitivity of these strains to streptomycin and neomycin was similar, and these strains may be regarded as moderately sensitive to these two agents.

Clinical experience has shown that aureomycin, chloramphenicol, penicillin, and oxytetracycline are of value in the treatment of cutaneous anthrax, and the laboratory observations of in vitro susceptibility to these antibiotics correlate well with these therapeutic results. It might therefore be predicted on the basis of the laboratory tests here reported that streptomycin and neomycin would prove of value in the treatment of cutaneous anthrax.

Lederle Laboratories Division, American Cyanamid Company, donated aureomycin; Parke, Davis & Company, chloramphenicol; Heyden Chemical Corporation, streptomycin; Burroughs Wellcome and Company, polymyxin; Chas. Pfizer & Company, Inc., oxytetracycline, and The Upjohn Company, neomycin.

7. Miller, E. S.; Scott, E. B.; Noe, H. A.; Madin, S. H., and Henley, T. F.: Chemotherapy of Experimental Anthrax Infections, J. Immunol. **53**:371-379 (August) 1946.

MALOCCLUSION AND ITS EFFECT UPON ORAL MEMBRANES

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NEW ORLEANS

THROUGHOUT life the lips, the buccal mucous membranes, and the tongue are subject to constant movement, friction, and irritation. These tissues must therefore possess elasticity. Unfortunately, their elasticity varies with age; thus their ability to compensate for injuries and distortion varies in proportion, and as aging progresses, this ability diminishes. Insults to tissues are better tolerated in childhood, but as a person becomes older, even slight insults, if long continued, produce unwanted reactions.

The hard structures of the mouth undergo constant changes which shape the bite, the dentition, the lips, and the septum of the nose and affect swallowing, drainage of the ear canals, the facies, and ultimately the person's future. For example, the facial contours of Andy Gump or of Granny Cringe focus our attention in the comic strip, as did W. C. Fields's rhinophymatous nose in the movies.

In brief review, some of the pathological changes observed in the lips are Fordyce's disease, hornblower's keratoses, acute and chronic cheilitis, fissures, leucoplakia, herpes simplex following exposure to heat or cold, granuloma pyogenicum, retention cysts, localized varicosities, nevi, verrucae, keloids, and malignant growths.

When the lips are opened, such disorders as marginal gingivitis, hypertrophied gums of the hippopotamus type—the edematous, erythematous, spongy, and bleeding gums that accompany pregnancy—anemias, drug or chemical toxemias, epulis between the teeth or in the spaces of missing teeth, granuloma fissuratum, and hemangiomata may be seen.

On the buccal membranes, changes such as the leucoplakia are found, and in addition, the snuff and tobacco plaques, fibromata, excoriations, and hemorrhagic puncta from chewing the side-wall of the mouth; on the lingual side of the teeth, torus palatinus or torus mandibularis glandular hypertrophy of the palate from the vacuum of the dentures or hyperkeratoses from loose dentures may be present.

Involving the tongue, there are varicosities, fibromata, nevi, granuloma pyogenicum, ulcers, tender and denuded areas, lingual tonsillitis, or carcinomata.

In this mouthful of disorders, none is so rare as to attract undue attention, but many of the disorders are ultimately so serious that it may well be asked, How does so simple a thing as malocclusion contribute to them?

First, notice how the open-bite (a condition of molar occlusion with failure of central and lateral occlusion) causes the lips to be dry because of mouth-breathing as well as faulty apposition. Subsequently, speech difficulties may ensue. The

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vertical overbite, or overjet, leaves an open space to be closed by the lips (Fig. 1). In this attempt at closure by the lips, the upper teeth rest on the lower lip and make an indentation there, and during sleep, when the lips are relaxed and the closure is even more inadequate, mouth-breathing will result, causing dryness, plus or minus the spread of the tarry distillate of tobacco over the indented fissured surface of the lips, thus furnishing the groundwork for the inception of pathological changes. The overbite may have had its origin from nasal or postnasal congestion or obstruction which forced the palate up, made the arch more acute, and caused the front teeth to protrude longitudinally.

Now, suppose the subject has a prognathous jaw with a prominent mandible or has lost back teeth and the mandible has drifted forward, causing a reverse overbite

Fig. 1.—Overbite.

(Fig. 2) and forcing the lower lip out past the protective plane or shadow of the upper lip. Drying exposure to direct sunshine and rubbing against the regular or irregular lower teeth make our tarpon-lipped patient a fit prey for atrophic plaques, leucoplakia, leucokeratoses, ulcerated herpes scars, hypertrophied buccal edges, and epitheliomata.

Therefore it is evident that either overbites or reverse overbites cause undue exposure and trauma to the lower lip.

The closed bite may result from worn teeth or from lack of dentures, since both of these shorten the distance between nose and chin. This gives the lips a horizontal, slit-like appearance (Figs. 3 and 4), causing loss of facial contour, pleats in the facial muscles, deeper wrinkles, buccal folding, and perlèche with or without implantation of Candida, as described by Finnerud.[1] Besides protrusion of the lips, the mandibular condyle may press upon the eustachian canal or pull on the pterygoid

1. Finnerud, C. W.: J. A. M. A. **126**:737 (Nov. 18) 1944.

Fig. 2.—Reverse overbite.

Fig. 3.—Deep bite—wet corners.

muscles, thereby causing the opening of the canal to become deficient, which results in inadequate drainage, which may in turn contribute to deafness and dizziness and may hamper swallowing. Bierman and Brickman [2] found that 28% of air cadets who suffered from ear blockage had malocclusion, and that in many the ear blockage was relieved when the malocclusion was corrected. The depressions or gaps left by missing teeth may prove a source of irritation because the tongue, lingual tonsils, and buccal or lip membranes are constantly forced in and out of these spaces. With horizontal overbite in the molar regions, there may be irritation and excoriation of either the buccal or the lingual tissues. Splints or acrylic guards may be worn to prevent this trauma.

All of the teeth are necessary—the front ones with which to bite, the bicuspids with which to crunch hard or brittle food and to mesh in order to prevent drifting

Fig. 4.—Deep bite—no or worn dentures.

of the mandible, and the molars with which to grind the food. In order to maintain alignment, all the teeth are needed, and any loss or alteration means loss of efficiency.

The sharp edges of ragged, rough, or crusted teeth often cause piercing injuries through which epithelial abnormalities and materials are carried into the deeper tissues, resulting in pathological lesions. A stray or irregular tooth may pierce a small varicosity, producing a well, or it may cause a healthy mucous duct to produce a retention cyst. Through the piercing injury, foreign material may be carried into the tissue and produce granuloma pyogenicum. Loosely fitting plates over poorly prepared, redundant ridges often stimulate granuloma fissuratum, or the plates may sway back and forth in a rotary motion and give rise to leucokeratoses or keratoses or to a hypertrophied granulation pad in the roof of the mouth.

2. Bierman, H. R., and Brickman, I. W.: Ann. Otol. Rhin. & Laryng. **55**:5 (March) 1946.

The production of malignant growths in the buccal cavity by any of the above-mentioned abnormal states should not be discounted. Malignant neoplasms of the lower lip occur predominantly in the male. However, they are common to both sexes in the molar, sublingual, and palate areas, or on the snuff locations, that is, between the lips and the teeth, and on the sublingual and maxillary-mandibular folds. Malocclusion and caries occur in a high percentage of these cases. Tobacco, anemia, and hypochlorhydria, I believe, play a part.

Exposure of the lips to trauma and to sunlight often precedes the development of herpes simplex. Biting the buccal wall or tongue precedes verrucae. Prominent multimetal fillings often set up electromagnetic irritations, as described by Dr. Lain, one of the discussors of this paper.[3]

Fig. 5.—Contour or profile pattern.

All these illustrations should lead the physician and the dentist toward action in preventive and corrective measures. A child who is mouth-breathing because of nasal obstruction, or who has an open-bite with resultant steeple palate and protruding upper teeth, should have the benefit of corrective measures before the mouth-breathing produces distorted lip membranes, cramped tongue, or speech defects. In the very young, if the nasal passage obstructions have been corrected, the orthodontist may be able to prepare the bony structure for the second set of teeth by the simple use of a bite-block. This approximates the arches and reduces the length of the arch, reduces the steeple palate, lengthens the upper lip, and corrects the facies. The orthodontist may advise removal of the bicuspids in order to shorten an upper or lower arch in the adolescent. In the adult, he may advise splints over the molars or over all the teeth to open the bite, or he may extract the front teeth in order to approximate the bite.

3. Lain, E. S.: J. A. M. A. **96**:771 (March 7) 1931.

Faulty, soft, and bony ridges should be prepared for dentures so that enough room for the tongue is assured and so that the lips will not be forced out of normal position.

Often the dentist can improve the appearance of the patient with malocclusion by giving partial or full dentures. I have observed such worn pancake dentures that a spot of the epithelium of the tongue was denuded by pressure and lack of space. Proper dental restoration should accompany the treatment of cheilitis, perlèche, leucoplakia, leucokeratoses, and cancers. Today, some dentists are so alert for the welfare of their young patients that they make profile pictures (Fig. 5), measurements, and bite models, so that in later years the patient can refer to these guides when wear and tear call for restoration. It is not enough to provide a sun protector for the lips; one should attempt to restore normal contour to them. Persons with deformities of the lips, the mouth-breathers and those with malocclusion, with inferiority complexes, have discovered that their dispositions improve and their complexes wane as the facies are restored to normal contour. They do not have to battle the complex; their mandible and lips may relax; and thus one agent of irritation has been eliminated from the many agents that cause pathological changes.

ABSTRACT OF DISCUSSION

DR. EVERETT S. LAIN, Oklahoma City: Before the last decade of medical programs, it was extremely rare to have heard such an enlightening dermatodental presentation as that given us today by Dr. Van Studdiford. Therefore I feel that he is to be highly commended for reminding us of the close relation that should exist between dentists and dermatologists in the study and treatment of oral cavity lesions. However, when we consider that the teeth and oral mucosa, genetically and anatomically, are closely related (each from the ectoderm membrane) to the cutaneous covering of the body, why should not dermatologists, of all medical specialists, be interested in the etiology and pathology of oral cavity lesions? Incidentally, I suspect that Dr. Van Studdiford is in daily or frequent association with some good orthodontist is his city.

May I join the author in reemphasizing the importance of a careful examination of the oral cavity of every patient, whether or not that patient is cognizant of any mouth disorder? By such routine examination, we will often meet with surprises and perhaps many times discover the key to the diagnosis of a skin eruption. Dr. Van Studdiford very appropriately calls attention to deformities of the face and their effect on the personality of the individual, even in his business or professional life, only because of some malocclusion or other dental defect which could have easily been corrected. He also called attention to a fairly common condition usually occurring in people past middle life, viz., subluxation of the temporomandibular joint which may cause a "click" and pounding of surrounding structures with resultant injury to the auditory nerve and other adjacent structures. He failed to mention one other injury, a most annoying symptom for which dermatologists as well as internists are so frequently consulted, that is, localized, persistent, burning tongue—glossodynia.

Several years ago Dr. J. B. Costen, of St. Louis, reported cases, proving that the condition may be traced to a traumatic injury or irritation to a linqual branch of the temporomandibular nerve which crosses around and, sometimes, over the temporocondyloid joint to supply sensation to the anterior two-thirds of the tongue, including the tip and also the mucosa of the lower lip.

Since attention was first called to this phenomenon I have made many such diagnoses and, with the aid of a qualified orthodontist, have likewise given complete relief to many patients. By a routine examination with one or two fingers over each condyloid joint, and with the patient instructed to open and close his mouth, it is surprising how often we may feel a sudden slipping of this joint, which even at times may be audible. This subluxation is usually caused by the loss of molars, and also the cuspids, which results in an abnormal fulcrum for mastication of food. After such a diagnosis and relief given by an expert dentist, the doctor as well as the dentist obtains the confidence and lasting gratitude of the patient.

Within my own practice perhaps the commonest disorder from malocclusion that I have observed is the smooth round, or maybe pedunculated, single or multiple tumors and fibromas always located adjacent to an irregular interspace between or where missing teeth occur. Such lesions rarely become cancerous, but since people are now cancer-conscious these tumors should be removed at once, preferably by surgical diathermy and coagulation of the base. Doubtless most dermatologists are now wise to the danger of cancer at any site in the mouth where long-existing trauma or irritation may have occurred. If cancer has already developed, it is usually advisable to treat the cancer before the teeth are extracted or other corrective methods instituted.

I agree with the deductions of the author that lesions as a result of electrogalvanism between heterogeneous metallic dental restorations are relatively rare, though, like focal infections, such lesions are easily overlooked unless the examiner is on the alert and is in possession of a sensitive electrogalvanic micrometer for testing.

I should like to report a few lines from a recent elaborate piece of research which has been done on this problem by Dr. William Schriever, Head of the Department of Physics, and Dr. Louis E. Diamond, Chairman of the Department of Biochemistry, of the University of Oklahoma School of Medicine. They have worked for two years by special request and under a grant from the Department of Research of the United States Navy. Their work is to be published soon in the *International Journal of Dental Research*. Briefly stated, they have proved, among other previously known facts, that bone fluid within the maxillae is equally as good a conductor of electric current as saliva. They have also arrived at the conclusion that visible injuries to the oral mucosa are relatively rare, though in some cases in which the subject exhibits a special sensitivity to metallic ions supplied by dental fillings in the presence of galvanism, there might be exerted an indirect detrimental effect on the mucosa of the oral cavity, since the current hastens the solution of metallic fillings and thus assists in transporting metallic ions to the tissues.

Dr. John F. Madden, St. Paul: I enjoyed Dr. Van Studdiford's paper and his humor very much. It should be emphasized that the attempt to correct malocclusions should be done early in the patient's life because at that time the corrections are more easily accomplished and are usually less expensive. Early corrections may prevent some of the more serious diseases discussed in Dr. Van Studdiford's paper.

Dr. Martin T. Van Studdiford, New Orleans: I want to thank Dr. Lain for bringing our attention to the problem of burning tongue. Often aberrant nerves are caught in scar tissue following extractions, causing a burning sensation of the tongue. Pressure from dentures or in the mandibular angle should be suspected. Dr. Martin Engman Sr. wrote about burning tongue, and he probably directed Dr. Costen's attention to the malady, as they are both from St. Louis.

As Dr. Madden has suggested, one difficulty encountered is the fact that most corrections should have been done in youth—bite blocks at 6 to 10 years and most corrections started before the 18th year. However many patients up to the age of 30 are having their malocclusions corrected. Opening the bite is being done on patients of all ages in two ways: one by placing an inlay on each tooth, the other by wearing either metal or acrylic appliances on the lower teeth that come in perfect apposition with the upper teeth.

Most of my information on reconstruction of the teeth has come from Schweitzer's text "Oral Rehabilitations." I regret that many of the Kodachromes which I showed cannot be used in the published paper.

OCHRONOSIS

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MINNEAPOLIS

OCHRONOSIS is a term which was first used in 1866 by Virchow,[1] who observed discoloration of various cartilages during a postmortem examination. Under the microscope, the pigment appeared pale yellow or ocher, although to the naked eye it was grayish-brown or black. Virchow's case remained unnoticed until Albrecht [2] reported a second one, in 1902. The cardinal features of the disease, consisting of blackening of the cartilages, pigmentation of the skin, urine that darkens on exposure to air, and osteoarthritis were described by Osler,[3] in 1904. Pick [4] reported a case, in 1906, which was supposedly due to the prolonged use of phenol dressings to ulcers of the leg. Cases of exogenous ochronosis (carbolochronosis), however, have not been seen for many years.

Medical writings of the 16th and 17th centuries referred to instances of urine which was black when voided or which darkened on exposure to air. Boedeker,[5] in 1859, found a reducing substance, not a sugar, in the urine of a patient with glycosuria, to which, on account of its behavior toward alkalis, he assigned the name alkapton. Wolkow and Bauman, cited by Smith,[6] termed the substance homogentisic acid because it was a homologue of gentisic acid. Alkaptonuria is a rare disorder, since less than 200 cases have been reported. In only about one-half the cases of alkaptonuria does ochronosis develop. Within the past several years, instructive articles have been written by Sugar and Waddell,[7] Smith,[6] Swirsky,[8] Mauser,[9] Friderich and Nikolowski,[10] Pomeranz, and associates,[11] and Eisenberg.[12]

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., April 24, 1952.

From the Department of Dermatology, University of Minnesota, H. E. Michelson, M.D., Director, and the Department of Dermatology, Minneapolis General Hospital, Carl W. Laymon, M.D., Director.

1. Virchow, R.: Ein Fall von allgemeiner Ochronose der Knorpel und knorpelähnlichen Theile, Arch. path. Anat. **37**:212, 1866.

2. Albrecht, H.: Über Ochronose, Ztschr. Heilk. **23**:366, 1902.

3. Osler, W.: Ochronosis, the Pigmentation of Cartilages, Sclerotics, and Skin in Alkaptonuria, Lancet **1**:10, 1904.

4. Pick, L.: Über die Ochronose, Berl. klin. Wchnschr. **43**:478, 1906.

5. Boedeker: Über das Alkapton, Ztschr. rat. Med. **7**:130, 1859.

6. Smith, J. W.: Ochronosis of the Sclera and Cornea Complicating Alkaptonuria, J. A. M. A. **120**:1282, 1942.

7. Sugar, H. S., and Waddell, W. W.: Ochronosis-Like Pigmentation Associated with the Use of Atabrine, Illinois M. J. **89**:234, 1946.

8. Swirsky, M. Y.: Ochronosis: Report of a Case with Alkaptonuria and Melanuria, Clinics **2**:1323, 1944.

(Footnotes continued on next page)

CLINICAL FEATURES

In ochronosis there is a brown or blue mottled discoloration of the skin of the neck, head, torso, and the extremities. In the axillae and the genital regions the skin may be bluish-green, due to pigment from the sweat and sebaceous glands. Pigmentation of the fingernails is rare. Discoloration of the lids, the conjunctivas, and the oral mucosa has been reported.

Ochronosis is frequently recognized by a blue discoloration of the ears. The darkened cartilages feel abnormally firm, and sometimes the ears feel rigid and nodular. The nose may be similarly involved, as well as the knuckles of the hands and the thenar and hypothenar eminences. Granular or diffuse deposits of pigmentation may be found in the costal cartilages, the intervertebral discs, the epiglottis, the trachea, the larynx, and the cartilages of the larger joints. The cartilages of the smaller joints are usually not pigmented. The perichondrium, the periosteum, the tendons, the fascia, and the capsules of the joints are usually less intensely affected.

Pigment may be deposited in the endocardium, the large blood vessels and kidneys, and, rarely, in the tonsils, the connective tissues of the lungs, the thyroid gland, and the dura mater. Endocarditis has been demonstrated in a number of cases in which postmortem examinations were performed. Black pigmentation of the cardiac valves as well as of the intima of the aorta and the iliac arteries has been noted in several instances. Hepatic lesions are unusual.

Young [13] reported prostatic calculi in a patient who had ochronosis. He could find only six other cases in which such lesions were present. He stated that a number of cases of renal calculi associated with ochronosis had been reported.

Smith [9] thoroughly discussed ochronosis of the scleras and corneas. He believed that superficial pigmented spots in the corneas near the temporal and nasal limbi represented a finding which was diagnostic of advanced ochronosis. Scleral ochronosis usually develops simultaneously with pigmentation of the cartilages of the ear. Skinsnes reported an instance of enucleation of an eye of a patient suffering from ochronosis, whose other eye had previously been lost traumatically. The enucleation was performed because of a misdiagnosis of the ocular ochronotic pigmentation as malignant melanoma.

Patients with ochronosis present a rather characteristic picture. They appear to be poorly nourished and debilitated. In many instances, they assume a posture characterized by the head thrust forward so that the muscles of the neck appear to be unduly prominent. The chest is large and somewhat emphysematous. The torso is held rigid, and the vertebral column is fixed. There is dorsal kyphosis, and the lumbar curve is either accentuated or obliterated. The arms hang limply

9. Mauser, C. L.: Alkaptonuria, J. A. M. A. **146**:815, 1951.

10. Friderich, H., and Nikolowski, W.: Endogene Ochronose, Arch. Dermat. u. Syph. **192**: 273, 1951.

11. Pomeranz, M. M.; Freidman, L. J., and Tunick, I. S.: Roentgen Findings in Alkaptonuric Ochronosis, Radiology **37**:295, 1941.

12. Eisenberg, H.: Alkaptonuria, Ochronosis, Arthritis, and Ruptured Intervertebral Disc: Complicated by Homologous Serum Reaction, Arch. Int. Med. **86**:79, 1950.

13. Young, H. H.: Calculi of the Prostate Associated with Ochronosis and Alkaptonuria, J. Urol. **51**:48, 1944.

by the sides. The thighs are flexed slightly at the hip, and locomotion is slow. When the patient walks, the entire lower extremity moves *in toto*. The feet are held in inversion and abduction.

Arthritis of the spine, pelvis, shoulders, knees, and hands is one of the most important signs of ochronosis. Soderbergh [14] described alternating areas of osteoporosis and osteosclerosis of the spine to which he applied the name "osteitis deformans alkaptonurica." Extensive calcification of the intervertebral discs may occur. Similar calcification may be noted in the tendon sheaths, the bursal sacs, and the synovial membranes. When ochronotic pigment is deposited in articular cartilage, the cartilage loses its elasticity, becomes brittle, and shows little resistance to mechanical strain. It cracks easily into small black fragments, which are wrenched off into the joint and soon become attached to the synovial membrane. Granulation tissue forms, and, eventually, after the cartilage remains lying as dead material in the synovial membrane, the fragments become absorbed and finally disappear. Hertzberg [15] reported capsular osteomas. Ankylosis of various joints may occur. Ochronotic patients with osteoarthritis are frequently subject to fractures resulting from minor injuries.

Falsely positive results of serologic tests for syphilis may be associated with the disorder.

In ochronosis, the urine may be normal in color when freshly voided but gradually turns black upon exposure to air, because of the polymerization of homogentisic acid to a black insoluble pigment of high molecular weight. Alkaptonuria is usually detected clinically by the history of black stains on diapers or underclothes. Dysuria is occasionally noted. Homogentisic acid is a strong reducing agent and will reduce Benedict's and Fehling's (alkaline cupric tartrate test solution) solutions. As a result, patients with alkaptonuria are often treated as diabetics until the correct diagnosis is established. Homogentisic acid is easily differentiated from glucose, because of its lack of optical activity and its failure to undergo fermentation reactions. Homogentisic acid will not reduce an alkaline bismuth solution such as Nylander's reagent and does not ferment yeast. The acid forms a black precipitate when 10% sodium hydroxide solution is added to urine containing it, and a deep-blue color develops for a moment upon the addition of a dilute of ferric chloride. When a drop of alkaptonuric urine which has been made alkaline is placed on sensitized photographic paper, the paper immediately turns black. Such a change does not occur with normal urine.

HISTOLOGIC FEATURES

In the skin of a patient with ochronosis, the epidermal changes are unimportant. There are varying amounts of homogeneous light-brown pigment in the cutis which displace the connective tissues. In some instances, the material is distributed rather diffusely, while in others it is clumped into round oval masses. Although the pigment is the same color as melanin, it does not stain with silver nitrate and becomes jet-black when stained with polychrome methylene blue. Friderich and

14. Soderbergh, G.: Zur Klinik der Alkaptonurie, insbesondere über die Wassermannsche Reaktion und Ostitis deformans alkaptonurica, Nord. med. **48**:19, 1915.

15. Hertzberg, J.: On Osteoarthrosis Alkaptonurica (Ochronotica) with Description of One Case, Acta radiol. **26**:484, 1945.

Nikolowski discussed the case of a woman who had ochronosis and who presented blue nodules on the cheeks which apparently were nevi. Five biopsies were performed of the skin and cartilage of the ear and of several nevi on the face. Ochronotic pigment was demonstrated in the cartilage of the ear and in lesions on the forehead and cheeks, which clinically suggested blue nevi. Melanin, however, was not found. Metaplastic formation of bone was found in one of the sections from the skin, along with large amounts of ochronotic pigment.

Skinsnes found that the pigment in cartilage was best stained by Masson's trichrome method. It appeared light-yellow to brownish-black, depending upon the amount which was present. It was homogenous and not evidently particulate. In the cartilage, the periosteum, the aorta, and scarred areas of the spleen and

Fig. 1.—Mottled pigmentation of face; bilateral pigmented spots on the corneas.

heart it varied but slightly in form. Where only a small amount was present, it was fine and diffuse and definite particulate form could not be seen microscopically. Where it was denser, it was more particulate, though it stained the cartilagenous matrix diffusely. Lying in connective tissue, it stained collagenous fibers yellow, but where particulate it was often contained in macrophages, though at times it was also free in the tissues.

REPORT OF A CASE

J. Z., a white man aged 71, died at the Minneapolis General Hospital on May 26, 1950. He had been admitted on several previous occasions. In March, 1950, he was discharged, but he was readmitted on April 17 for evaluation of a pigmentary disorder which had been noted about 20 years previously. He also stated that he had had arthritis of the extremities, hips, and spine for about 30 years. His father, mother, two brothers, and one sister all had normal skin.

Physical examination showed a man who had a chronic debilitating disease. He stood with a decided stoop, his head was thrust forward, and his arms hung limply at his sides. The skin

Fig. 2.—Pigmentation on hands, especially over tendons.

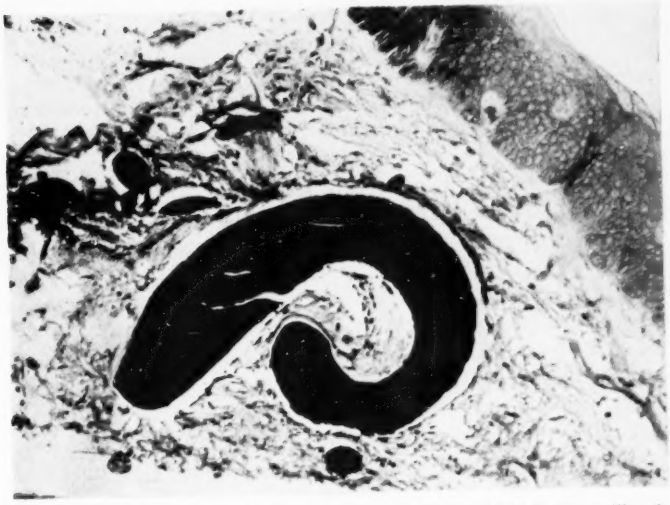

Fig. 3.—Masses of pigment in cutis. Note the bizarre form, which is not unlike the encapsulated larva of the Trichinella spiralis. Polychrome methylene blue stain; × 115.

of the face, neck, and chest showed a peculiar mottled pigmentation. Most of the affected areas appeared brown, although the nasal tip and the ears were blue. There were linear streaks of bluish-brown pigmentation which seemed to overlie the tendons or the dorsal surfaces of the hands. Both scleras were the color of slate, and there were dark-blue pigmented spots in the corneas superficially near the temporal and nasal limbi of both eyes. X-ray examination showed calcification of both ears. X-rays of the knees showed a rather severe bilateral hypertrophic arthritis, with narrowing of the cartilages but with no signs of calcification. Studies of the cervical spine showed evidence of ankylosing arthritis. Although the intervertebral discs were narrowed, they were not calcified. The dorsal spine showed rather severe arthritis. A film of the chest showed cardiac enlargement of the left ventricular type. Results of serologic tests for syphilis were negative. The findings of the glucose-tolerance test were normal, and no sugar was found in the urine.

The patient had chronic prostatitis and cystitis, and his urine contained albumin, pus cells, erythrocytes, and casts, on many examinations. The color of the specimens which were freshly voided varied from amber to brown. Within 48 hours the urine turned black on exposure to light. Tests for homogentisic acid by exposure of the urine to light, heating after the addition of 5% KOH, and the addition of ferric chloride gave positive results.

Several biopsies were performed on the skin overlying the face and hands. The histologic findings were identical to those previously described.

Postmortem examination showed the aforementioned cutaneous pigmentation. The root of the aorta presented black pigmentation, and there was a slight amount of calcification irregularly distributed over its surface. The entire artery was tortuous and showed a gray pigmentation throughout its entire length. The mitral valve was calcified and presented irregular leaflets. The cartilages of the thoracic cage were black and moderately calcified. There was definite enlargement of the distal ends of the femurs and the proximal ends of the tibias, indicating an old arthritic process. Both knees were deformed, and there was hypertrophic spurring of the vertebral bodies, with considerable scoliosis. The intervertebral discs were black.

Microscopic examination showed dense polymorphonuclear infiltrate around all the bronchi. There many macrophages which contained a gold-colored pigment intermingled with black granules. The media of the aorta was brown and contained many granules of black pigment, and there were deposits of calcium in the intima. The prostatic concretions were also black. The Kupffer (stellate) cells in the liver contained granules of black pigment. Similar granules were found in the endothelial cells of the spleen.

COMMENT AND SUMMARY

Alkaptonuria literally refers to the occurrence in the urine of a substance which has "an affinity for alkali." This term arose from the fact that the urine of patients with alkaptonuria undergoes a rapid spontaneous oxidation in the presence of alkali. The urine in human alkaptonuria contains 2,5 dihydroxyphenylacetic acid or homogentisic acid. Before speaking about the specific metabolic block in alkaptonuria, it would be well to mention briefly our present knowledge of the intermediary metabolism of tyrosine.

According to Fitzpatrick [16] and Lerner,[17] tyrosine, or parahydroxyphenylalanine is metabolized at different sites in the body to three biologically important compounds. In the thyroid, tyrosine is heavily iodinated and ultimately forms thyroxin. In the adrenal medulla, tyrosine is converted into epinephrine and nor-epinephrine. Human pigment cells also convert tyrosine into melanin. All three of these reactions have been proved conclusively with radioactive compounds. The tyrosine to melanin reaction in human pigment cells was recently proved by Fitzgerald and Lerner with the use of radioactive C^{14}-labeled tyrosine. In addition to the three afore-

16. Fitzpatrick, T. B., and Lerner, A. B.: Personal communication to the author.

17. Lerner, A. B., and Fitzpatrick, T. B.: Biochemistry of Melanin Formation, Physiol. Rev. **30**:91, 1950.

mentioned pathways, tyrosine undergoes oxidative deamination to parahydroxyphenyl pyruvic acid, and later another hydroxyl group is inserted, and still later rearrangement occurs, forming homogentisic acid. This is further broken down by opening of the benzene nucleus, with the formation of acetoacetic acid and fumaric acid, and ultimately carbon dioxide and water. These steps have been proved conclusively by Lerner using C^{13}- and C^{14}-labeled tyrosine and phenylalanine. In alkaptonuria the degradation of homogentisic acid does not occur and the compound accumulates in the extracellular fluids, where it undergoes spontaneous oxidation to a dark-colored insoluble product. Homogentisic acid, for some as yet unknown reason, selectively localizes in cartilage. Normal cartilage placed in homogentisic acid (a colorless solution) gradually darkens to a black color. The fibrous tissue surrounding the cartilage does not darken. This phenomenon explains the black cartilage, which is a cardinal feature of alkaptonuric ochronosis.

It should be emphasized that homogentisic acid is an intermediate in the catabolism of tyrosine by normal patients and does not accumulate in the extracellular fluids because it is converted to carbon dioxide and water. In the patient with alkaptonuria homogentisic acid accumulates because of the absence of one or more of the enzymes which normally bring about its degradation. It is well established that genes control enzyme synthesis. Alkaptonuria, which is a Mendelian recessive usually, and rarely dominant, probably results from the absence of a gene which brings about the synthesis of the enzyme or enzymes necessary for the degradation of homogentisic acid.

ABSTRACT OF DISCUSSION

Dr. Michael H. Ebert, Chicago: We are all obligated to Dr. Laymon for his thorough study of a very rare disorder. I saw this patient at Dr. Laymon's clinic in Minneapolis. This is the only example of ochronosis that I have ever seen. Dr. Laymon has covered the subject so thoroughly in his paper that little remains for me except a few reflections and speculations.

Ochronosis, as Dr. Laymon has just told you, is due to incomplete degradation of tyrosine down to carbon dioxide and water. The process is halted with the production of homogentisic acid. The enzyme necessary to activate the next step is lacking. The retained homogentisic acid is stored as an insoluble product closely resembling melanin, in, among other places, the cartilage and the skin. This results in the peculiar pigmentation, so well demonstrated in this case, that makes the disorder a subject of interest to us as dermatologists. The absence of the gene or genes which control the formation of this enzyme is probably due to the appearance of a biologically defective mutant. Undoubtedly, in the course of human evolution there have appeared many mutants characterized by the absence of a gene or genes controlling one or another of the numerous enzymes involved in our complex metabolism. Such mutations or such mutants have been extensively studied by plant pathologists in fungi pathogenic for plants. They can be studied because the conditions are very simple. The lack of any important enzyme is usually lethal for the organism; consequently, the mutant is not preserved by heredity. In ochronosis the associated invalidism which Dr. Laymon has so well described appears late enough in life to permit reproduction of the trait. The trait, as he stated, is a Mendelian recessive in most instances and is extremely rare. It would be much rarer were it not for the intermarriage of conductors of this particular trait. Garrod, in his text, "Inborn Errors of Metabolism," reported alkaptonuria in 13 families. In six of these families the parents were cousins. The mutant which results in ochronosis has apparently appeared independently on more than one occasion. Only in this way can we account for the appearance of the trait as a dominant in Pieter's series, in which it appeared in four generations. In nearly every other case reported the trait is a recessive. This would seem to indicate that the absence of the enzyme had appeared as an independent mutation in Pieter's series.

Two other examples of disorders probably due to the absence of an enzyme are cystinuria and pentosuria. In either case the trait causes very little disturbance to the person; consequently it is preserved. These disorders are also recessives and are extremely rare.

Dr. Fred D. Weidman, Philadelphia: Two years ago a section of ochronosis was exhibited at the meeting of the American Academy of Dermatology and Syphilology, at its round table on histopathology, and at that time I wondered what particular structure of the skin it was which had been stained, so to speak, by the homogentisic acid. The rounded configuration and the multiple rib-like fractures reminded one somewhat of colloid degeneration, but the color was, of course, entirely different. I assume that this mass of solid deeply pigmented substance is not 100% homogentisic acid. The implication is that there must be some kind of a relatively dense substance (it reasonably cannot be cartilage) in the skin, but may I ask Dr. Laymon what he thinks the origin and pathogenesis of these masses are.

Dr. Carl W. Laymon: I should like to thank Dr. Ebert and Dr. Weidman for their discussion. We had hoped to experiment with tyrosine labeled with C^{14}, but the patient died before we had an opportunity.

The pigment in ochronosis is probably a polymerized product of homogentisic acid of high molecular weight. It is not melanin.

DERMATOLOGICAL MANIFESTATIONS OF FAMILIAL AUTONOMIC DYSFUNCTION (RILEY-DAY SYNDROME)

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AND
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A CURSORY review of dermatologic literature indicates that the Riley-Day syndrome is not known. In the past a number of children have been seen by hospital services and private physicians presenting "symptoms so puzzling as to defy exact diagnosis yet so similar as to constitute a clinical entity."[1]

This syndrome is characterized by the following more or less constant features: (1) Jewish extraction, (2) defective lacrimation, (3) skin blotching, (4) excessive perspiration, (5) drooling, (6) emotional instability, (7) motor incoordination, (8) hyporeflexia, (9) relative indifference to pain, (10) hypertension, (11) cyclic vomiting, (12) frequent pulmonary infection, (13) frequent unexplained fever, (14) breath-holding spells in infancy, (15) urinary frequency, (16) mental retardation, (17) convulsions, and (18) corneal ulcerations.

In August, 1952, Riley reported 33 cases,[2] in 10 of which the patients died, and in which autopsy had been performed on nine. Riley proposed the term "familial autonomic dysfunction," since this clinically distinctive entity has not been hitherto described in medical literature. Other syndromes such as diencephalic autonomic epilepsy,[3] postencephalitic parkinsonism,[4] and Page's syndrome[5] differ from the syndrome in discussion in one or more of the relevant features or in the presence of significant autopsy findings.

The following case is presented to call attention to a dermatologic clue in a serious internal disease.

REPORT OF A CASE

History.—K. S., 14½ years of age, is an apparently healthy and well nourished white girl whose dermatologic symptom consists of intermittent skin blotching.

The patient's parents are American-born and of Jewish extraction and in a satisfactory state of health. The findings of their past history are essentially negative. One brother of

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Presented at the meeting of the New York Academy of Medicine, Section of Dermatology and Syphilology, Dec. 2, 1952.

1. Riley, C. M.; Day, R. L.; Greeley, D. M., and Langford, W. S.: Central Autonomic Dysfunction with Defective Lacrimation: Report of 5 Cases, Pediatrics **3**:468 (April) 1949.

2. Riley, C. M.: Familial Autonomic Dysfunction, J. A. M. A. **149**:1532 (Aug. 23) 1952.

3. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

4. Ostow, M.: Recurrent Autonomic Phenomena Associated with Exacerbations of Postencephalitic Parkinsonism: Report of Case, Arch. Neurol. & Psychiat. **50**:342 (Sept.) 1943.

5. Page, I. H.: Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, Am. J. M. Sc. **190**:9 (July) 1935.

the patient was found dead in his crib at the age of 7 months. Permission for an autopsy was not granted. The cause of his death was attributed to an enlarged thymus gland. The patient has a sister, aged 10½ years, and a brother, aged 2½ years, both in good health. The patient was born at full term and weighed 7 lb. 9 oz. (3,430 gm.). Immediately after birth the patient was placed in an oxygen tent for six days because "she swallowed a lot of mucus," and an acute respiratory disturbance developed. She was fed both by breast and by formula and continued to grow normally.

At 8 weeks of age she held up her head, at 6 months of age she sat up alone, at 15 months of age she talked, and at 2 years of age she walked.

Early in her neonatal period one outstanding feature was noted: There was an absence of tears. The patient has since her birth never cried with tears.

It was at the age of 6 months that she again needed medical attention for an upper respiratory condition that was accompanied by fever. From then on she continued to have frequent bouts of unexplained or explained fever, and she had had, up to the age of 9 years, 12 attacks of lobar, bronchial, and virus pneumonia. At about this age (6 months old), an unusual degree of blueness and dampness of the infant's hands and feet were noted.

At the age of 9 months the patient began to hold her breath, her face became cyanotic, and muscular rigidity with unconsciousness occurred. These spells continued for seven years, once daily when she was at home and three times daily when she was at her grandmother's.

Her skin blotching was noted for the first time at the age of 14 months and tentatively diagnosed as the erythema of scarlet fever. These cutaneous symptoms, in the form of sharply defined erythematous maculae of the size of a nickel and a quarter on the entire face and of less discrete larger ones on the neck, upper chest, arms and waistline, have persisted to date and appear consistently with excitement and eating of her favorite food.

As an infant the patient vomited very easily, at least 3 times daily, mostly in a projectile manner. To be ready for such emergencies, a bowl was placed next to her on the table until she was 5 years of age. She vomited especially frequently at times of emotional upsets and physical illness, necessitating up to the age of 5 years frequent rectal and intravenous feeding. Her parents estimate that she had had about 100 separate cycles of vomiting, many lasting from four to eight days. The most recent bout occurred on the day following her presentation at the New York Academy of Medicine, when she vomited the entire day.

When crying or excited, from infancy up to the present time, she perspires so profusely that her clothes have to be changed.

The patient began menstruating at the age of 11 years.

Except for a generally poor muscle coordination, the patient's physical development was and is within normal limits. The parents state that since babyhood she walked with a "painful gait—as if she would have marbles in her shoes." Her muscular balance has been so precarious that anyone rushing past her with the slightest amount of force (on stairs for instance) would make her topple over. Even today she has a peculiar shuffling "flat-footed" gait.

The patient has been known not to mind pain. At the age of 2½ years, for instance, a heavily bleeding inch-long (2.5 cm.) scalp laceration went unnoticed for a rather long time. She never complained about the pain or the physical discomfort associated with the unusually large number of parenteral administrations that she has received to date. She was completely indifferent to pain caused by the cold pressor test.

At the age of 7 years her blood pressure was found to be very elevated. From then on to date readings have been taken and they reveal extreme fluctuation, from 64/58 mm. to 220/120 mm. It is interesting to note that her blood pressure is lowest while standing, higher when sitting, and highest when lying down.

The patient's blood pressure has always been higher when she was alarmed or during the episodes of vomiting, and of such variable character that walking from her bed to the bathroom in the morning would cause such severe hypotension that she would suffer from "blackouts." At present, she is forced to sit a while in bed before getting up and thus apparently brings her arterial tension to a more tolerable level and successfully avoids her blackout spells.

She has been a happy child, though she would become easily excited. This emotional overreaction to simple stimuli has persisted to date and often alternates with little or no response at all to impressions of all sorts. The duration of the patient's attention to school work, tele-

vision, and other interests has always been brief. She never withdrew from contact with playmates, although her opportunity to mix with children has not been very ample, since her frequent attacks of illness necessitated home tutoring.

After her fifth year of life, she was hospitalized several times for study and therapy. At the Mount Sinai Consultation Service, New York City, at the age of 5 years, she was given skin tests for allergy, with negative results. She was also thought to have bronchiectasis, and bronchoscopy was suggested as a diagnostic and therapeutic measure. At the age of 6 years this procedure was performed at the Beth Israel Hospital, New York City, and no evidence of bronchiectasis was found. At the age of 7½ years, a bronchoscopy was again performed at the Jackson Memorial Hospital, in Florida, and again the results were negative. At 8 years of age she was hospitalized for ulcerative stomatitis.

At the age of 9½ years, a private physician found her sedimentation rate to be very rapid (54 mm. and later 85 mm. per hour) and hospitalized her for further study and treatment.

At the age of 13 years, the patient was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, with the diagnosis of rheumatic fever. Here she underwent a whole group of diagnostic tests, from routine laboratory studies and x-ray examinations including intravenous pyelograms to electroencephalograms, cold pressor tests, the benzodioxane test for hypertension due to circulating adrenalin[6] and perirenal air insufflation for pheochromocytoma. The results of all the examinations were essentially negative.

On June 18, 1952, surgical exploration for pheochromocytoma was undertaken, with completely negative results.

When the patient was seen by one of us (Dr. Rubin) on Dec. 1, 1952, the physical findings included the following salient points: Her skin was cold and damp. Her deep reflexes were either absent (knee jerk) or else were obtained greatly diminished and only with reinforcement. Her skin blotching began to appear on attempts to elicit her reflexes and later upon other emotional stimuli, such as questioning her about her menstruation. Sharply circumscribed patches appeared on both sides of the forehead approximately of the same size and number, but paler on the right side of the forehead. Maculae also appeared on the neck, upper chest and arms. Upon cessation of stimulation (completion of physical examination) blotching would cease. She exhibited a shuffling gait, although the arches of her feet were found to be very good. She had urinary frequency. The conjunctiva and sclera appeared normal. Examination with fluorescein disclosed no corneal ulceration. The blood pressure read as follows: standing 100/80 mm., sitting 150/80 mm., and lying down 200/120 mm. Intellectually, the patient appeared to be superior.

The findings of the rest of the physical and neurological examination were essentially negative.

Diagnosis.—The diagnosis in the presented case as well as in all other fairly typical cases of this syndrome may be easily made by looking for the outstanding features (Table).

Routine studies and special tests were apparently of no particular diagnostic value.

Treatment.—Dermatologic manifestations. This patient receives no specific dermatologic treatment, since no such therapy is available at present or is particularly indicated.

Syndrome: The treatment unfortunately is symptomatic.

This patient, after prolonged stays in different climates and countless unsuccessful therapeutic attempts, is at present under the care of her private physician, who employs medicinal aids (veratrum viride; hydralazine hydrochloride, etc.) and minor psychotherapeutic measures and carefully supervises her daily activities.

Some of the heroic efforts to stop the episodes of cyclic vomiting, in the cases reported by Riley, included splitting the tentorium, prefrontal lobotomy, lumbar sympathectomy, and electric shock therapy, in addition to measures such as parenteral fluids and blood transfusions that have been used in the case presented. Attempts at psychotherapy were unsuccessful, because no contact with the patients could be established. Among the host of various drugs which were tried, therapeutically or prophylactically, without any success, were cortisone, dimenhydrinate (Dramamine), anticonvulsants, muscle relaxants, and autonomic-active drugs.

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6. Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, J. A. M. A. **135**:971 (Dec. 13) 1947.

COMMENT

The foregoing case represents a rather typical example of familial autonomic dysfunction, as evidenced by the facts presented in the Table. The common features of this condition, as grouped by Riley, are enumerated in the left-hand column of the following table and those occurring in the presented case are in the right-hand column.

Autopsy findings of nine cases did not further understanding of the nature of this disease.

Cyclic vomiting and drooling are outstanding features in the presented case. Note that excessive salivation may have caused aspiration pneumonia or at least an acute respiratory embarrassment in this patient in her earliest neonatal period. In eight of Riley's cases death was attributed to aspiration pneumonia.

Occurrence of Features

According to Riley	In This Patient
Almost Constant Features	
1. All of Jewish extraction (100%)	Yes
2. Defective lacrimation (100%)	Yes
3. Skin blotching (97%)	Yes
4. Excessive perspiration (100%)	Yes
5. Drooling (100%)	Yes
6. Emotional instability (100%)	Yes
7. Motor incoordination (100%)	Yes
8. Hyporeflexia (97%)	Yes
9. Relative indifference to pain (100%)	Yes
Not Constantly Present Features	
1. Hypertension, intermittent (85%)	Yes
2. Cyclic vomiting (63%)	Yes
3. Frequent pulmonary infection (74%)	Yes
4. Frequent unexplained fever (67%)	Yes
5. Breath-holding spells in infancy (73%)	Yes
6. Urinary frequency (75%)	Yes
7. Mental retardation (55%)	No
8. Convulsions (50%)	No
9. Corneal ulceration (35%)	No

Vomiting and breath-holding in many cases, including the one presented, ceased when the patients were in the hospital wards, pointing out the psychic relationship of these symptoms.

Obviously, most of the symptoms are caused by a dysfunction of the autonomic nervous system. Some, however, such as poor muscle coordination, hyporeflexia, and mental retardation (a symptom absent in the presented case) are of neurologic origin. Thus, the bulk of clinical evidence would suggest a centrally localized etiology.

With regard to familial incidence, it is of interest to mention that among Riley's 33 cases there are four pairs of siblings. Although it is speculative to say so, the clinically assumed "thymus death" of this patient's deceased infant brother may have been due to some disturbance on the basis of familial autonomic dysfunction.

From a dermatologic viewpoint, it must be emphasized that familiarity with this clinical entity and its cutaneous manifestations may greatly aid in the recog-

nition and solving of an otherwise difficult differential diagnostic problem. It must be remembered that familial autonomic dysfunction may not be a medical curiosity. Although the syndrome is assumed to be congenital, unrecognized cases that have survived into adulthood might be found with wider dissipation of the presented facts.

SUMMARY

The presented case of familial autonomic dysfunction has all the common features: (1) Jewish extraction, (2) defective lacrimation, (3) skin blotching, (4) excessive perspiration, (5) drooling, (6) emotional instability, (7) motor incoordination, (8) hyporeflexia, (9) relative indifference to pain. In addition, the patient also exhibits seven of the less constant features.

Clinical diagnosis of this presumably congenital and genetic disease is not difficult.

The dermatologic findings of erythematous maculae are persistent and occur consistently on the same sites when the patient is excited.

STRESS DERMATOSES

Suggested Integration of the Allergic-Psychogenic Dermatoses

HARRY L. ARNOLD JR., M.D.
HONOLULU, T. H.

THE SOLE purpose of this presentation is to suggest a point of view from which one may regard a considerable number of dermatoses, many of which seem quite unrelated to one another, not as separate disease entities but as different facets of the same fundamental kind of disturbance of the normal state.

By this it is not meant that the disorders so regarded are all the same disease. They are still different diseases, with different manifestations, different treatments, and different prognoses. But curious similarities may be observed among them: One disease may have the same apparent cause as another; in many of them the cause is obscure, and in many it is believed to be either "allergy" or emotional tension, or both; transition from one disease to another may occur in some cases; transition from one cause to another may occur in some of the diseases; two or more diseases may occur either simultaneously or consecutively in the same patient with what seems more than chance frequency, and lessons learned in the management of one of these diseases may in many instances be applied to the management of others within the group. Though the theoretic basis of the point of view to be offered here is still obscure, it is becoming less so, and I have found the concept a valuable guide in the practice and teaching of dermatologic medicine.

THE STRESS MECHANISM

The expression "stress dermatoses" has already been applied by Hans Selye and by others to most of the diseases to be considered here, though not to all. Its essential meaning for our purposes is this—that the cause of the disease should be regarded not as only acting directly on the tissues in which the disease occurs but rather as acting (at least in part) indirectly, by suppressing the pituitary-adrenal mechanism of resistance, with the result that the tissues are permitted to follow their natural bent, whatever that may be.

This depression of the pituitary-adrenal axis may be produced by foods, bacterial toxins, drugs, emotional tension, or other "stressor" agents; this much of the picture has been extensively elaborated upon by Selye and by other writers. This view renders largely meaningless the familiar conflict between the allergist and the "psychosomaticist," because each is talking about a different variety of the same sort of etiologic agent, and both are right.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., April 25, 1952.

The response of the individual patient to or in this situation of pituitary-adrenal depression must be an extremely complex one, determined by many factors of which we know little. It seems possible that it may result, however, in the appearance of one or more of the following dermatoses:

Psoriasis
Neurodermatitis circumscripta
Atopic dermatitis
Seborrheic dermatitis
Pustular bacterid
Dermatitis herpetiformis
Pemphigus
Hydroa aestivale
Pompholyx
Dermatitis repens
"Dermatophytosis"
Moniliasis
Alopecia areata
Exudative neurodermatitis
Exfoliative dermatitis
Fixed drug eruption (and other drug eruptions)
The erythema group:
  Urticaria
  Erythema multiforme
  Variants
"Collagen" diseases:
  Lupus erythematosus
  Polyarteritis nodosa
  Dermatomyositis
  Scleroderma
Parapsoriasis
Vitiligo

I realize that the inclusion of some of these disorders in this category rests on a very shaky foundation; I can only plead that the whole concept is highly tentative and hypothetical. It is almost as likely, on the other hand, that the list is incomplete, and that other disorders will have to be added to it from time to time.

Ignorant as we are of the way in which these disturbances are caused, we do know a little of the probable determining factors, that is, the factors which determine which reaction will result from which cause—in some of them. We know, for example, that individual predisposition must be important, since the same cutaneous reaction is prone to occur repeatedly in the same person as a result of exposure to different causes. For instance, one may have atopic dermatitis from sensitivity to egg protein in infancy and continue to have it in childhood from emotional causes despite loss of the egg sensitivity or exclusion of egg from the diet. Another case in point is the old dermatologic proverb to the effect that if you scratch a psoriatic you'll find psoriasis.

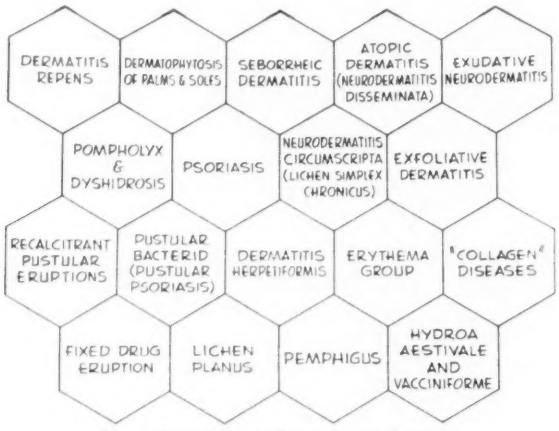
We know, furthermore, that some causative agents tend to elicit the same reaction in different persons; for example, sulfathiazole is likely to cause erythema nodosum rather than any other sort of skin reaction; acetylsalicylic acid (Aspirin) is prone to produce urticaria if it affects the skin at all, and circumscribed neurodermatitis is more apt to be on the basis of emotional conflict than on the basis of food allergy. Perhaps the pituitary-adrenal suppression varies qualitatively as well as quantitatively.

The relationship of various neurotic cutaneous reactions to specific kinds of emotional stress is a fascinating field which has been elaborated on rather extensively by Obermayer, who, for example, assigns psoriasis in general to suppressed hostility, urticaria to a sense of helplessness in an unhappy situation.

Some of the diseases being considered in this group have only one kind of cause: Fixed drug eruption, for example, is probably always due to drug hypersensitivity of a very specific and peculiar sort—related, mysteriously enough, to the occasionally observed capacity of these same drugs to depress the granulocytic cells of the bone marrow.

Examples of this sort could be multiplied almost indefinitely; those given will serve, however, to indicate the lines of thought along which further progress may be expected.

Assuming that we have assembled a number of skin diseases attributable to "stress," how can we now relate them to one another in some useful and integrated way? Let us consider them as a series of pairs of diseases, pairs in which we can find physical and perhaps physiologic resemblances and occasionally transition from one member to the other or vice versa. Here we will be on the most uncertain ground possible; what we are able to believe in this regard is the result of what we have been taught and of what we have seen happen, or believe we have seen. I can well imagine that what is to follow will be received with reactions ranging from complete incredulity to mild skepticism to, perhaps, qualified approval and, occasionally, acceptance.



Stress dermatoses; allergenic-psychogenic.

PSORIASIS AND PUSTULAR BACTERID

This pair, psoriasis and pustular bacterid, offers an easy starting point even for the skeptical. Some, no doubt, will say it is not a pair of dermatoses at all, but only a pair of synonyms, since it is possible to regard the palmar-plantar pustular bacterid of Andrews as an anatomic or morphologic variant, or perhaps a complication, of classic psoriasis.

Yet the pustular bacterid has two features which seem to distinguish it rather sharply from psoriasis, perhaps even from pustular palmar or plantar psoriasis, namely, spontaneous remissions and responsiveness to one or more sulfonamides or other antimicrobic agents or to the removal of a focus of infection. One cannot say that these features are never true of psoriasis, but certainly they are not regularly true of it. Despite this, it may happen that in a patient with a typical pustular bacterid psoriasis of the classic variety in the usual sites will develop, or that in a patient with classic psoriasis palmar lesions will develop which eventually become the only manifestation of the disease and which can be controlled with one or another of the sulfonamides.

Are they two diseases, then, or one? I think that they are two, but they are by no means as distinct from one another as two diseases are usually thought to be. The distinction is almost more semantic than medical. We can transfer from either disease to the other a few facts, such as essential incurability, probable limited controllability with inorganic arsenic (well-known for many decades, of course), probable limited controllability with corticotropin or cortisone, and liability to be caused or aggravated by not one but a variety of causative agents, including emotional factors and possibly also foods, drugs, physical or chemical trauma, or bacterial toxins. Yet, the likelihood of helping the victim of Andrews' bacterid by antimicrobic agents or by removal of foci of infection is so great that a useful, practical purpose is served by regarding the two as separate entities.

PUSTULAR BACTERID AND DERMATITIS HERPETIFORMIS

Like the first pair, the grouping together of pustular bacterid and dermatitis herpetiformis will startle few dermatologists. It seems an obvious kinship. Both diseases are characterized by essential incurability, chronicity, spontaneous remissions, recurrences *in situ*, grouped sterile vesicles, and often symmetry, pruritus, eosinophilia, and limited controllability by inorganic arsenic, sulfonamides, antibiotics, antihistaminics, corticotropin, or cortisone. Both are apparently occasionally cured by removal of foci of infection.

DERMATITIS HERPETIFORMIS AND PEMPHIGUS

A whole monograph could be written on the history and ramifications of the distinction between these two diseases, dermatitis herpetiformis and pemphigus, which were regarded as one until Duhring separated them nearly 70 years ago. It is unnecessary to elaborate on the differentiating features, which are familiar to every dermatologist. I wish only to allude to the cases, of which many of us have seen at least an example or two, in which either a young patient, originally thought to have pemphigus, later presents features of dermatitis herpetiformis, with a correspondingly good prognosis for life or in which an older person, believed to have dermatitis herpetiformis, begins to have mucosal lesions and in whom an obvious, perhaps fatal, case of pemphigus eventually develops.

The same diagnostic criteria that in general permit us to make an accurate prognosis and to select proper treatment must suggest strongly in the light of such cases as the ones mentioned above that there is no absolute etiologic or other distinction between the two diseases. They are probably related. Further evidence of this may be seen in the occasional apparent responsiveness of both disorders to treatment with heavy metals, and in their control by corticotropin or cortisone, or by *p*-aminosalicylic or *p*-aminobenzoic acids, as demonstrated by O'Leary, Zarafonetis, and others.

PEMPHIGUS AND THE ERYTHEMA GROUP

Erythema multiforme bullosum and ectodermosis erosiva pluriorificialis—to consider them for a moment together as representatives of the erythema group—have a great deal in common with pemphigus vulgaris: large vesicular lesions, generalized distribution with a predilection for mucous membranes, no specific

known etiologic agent, no specific curative treatment, potentiality for serious permanent damage (particularly to the eyes), possibility of a fatal outcome, and controllability, at least to a degree, by the antistress hormones and drugs.

The essential unity of the erythema group has not been seriously questioned since Osler began his definitive writings on this subject nearly 60 years ago. Urticaria, erythema nodosum, erythema exudativum multiforme, the whole medley of curious and unusual configurative and persistent erythemas, nodular vasculitides, and nodular panniculitis, etc., are all close relatives of one another. Closely related, too, though apparently on the other side of a boundary within the group, is anaphylactoid purpura, with or without cutaneous purpura.

THE ERYTHEMA GROUP AND THE "COLLAGEN" DISEASES

The close physical and pathologic-physiologic relationship between the erythema group and the "collagen" diseases is recognized by most physicians. Osler, in 1895, included systemic lupus erythematosus (though not by this name) with the erythema group, and the occurrence of ordinary erythema multiforme in some cases of systemic lupus erythematosus is familiar to most of us. The occasional apparent usefulness of antihistaminics in some diseases of both the erythema group and the "collagen" group, and the regular and sometimes spectacular effectiveness of corticotropin, cortisone, and *p*-aminobenzoic and *p*-aminosalicylic acids in both are new evidence of the affinity between the two categories. Further clinical similarities are plentiful; erythema nodosum and the other nodular vasculitides have a lot in common, both etiologically and pathologically, with polyarteritis nodosa, for example. The differences seem to be, in large measure, of degree rather than of kind.

HYDROA AESTIVALE; HYDROA VACCINIFORME

The distinctive, primarily photogenic disorder, hydroa aestivale (hydroa vacciniforme) does not lend itself especially well to pairing with other diseases in the group. Its major causative stress, sunlight, is of a specific sort, and its physical characteristics, aside from its having vesicles in common with pemphigus and with some cases of erythema multiforme, are unique. Still, it has been controlled by the exhibition of *p*-aminobenzoic acid (Zarafonetis, Curtis), and it seems probable that it belongs somewhere in this area. Its inclusion here is admittedly tentative.

PSORIASIS AND NEURODERMATITIS CIRCUMSCRIPTA

"Pairing" psoriasis and neurodermatitis circumscripta brings their respective diagnostic criteria into question. It is based on the following arguments: (1) Psoriasis in certain cases itches as intensely and paroxysmally as circumscribed neurodermatitis, (2) circumscribed neurodermatitis may be "psoriasiform," and in such instances particularly, (3) the histologic differentiation may be difficult and largely dependent on the presence of eosinophiles in neurodermatitis and their absence in psoriasis.

The difficulty of differentiating between the two diseases in a borderline case may be great, and the distinction may depend upon one's personal predilections regarding the weight to be given to various criteria. For example, can psoriasis be solitary? Can neurodermatitis circumscripta involve the elbows and knees? Whether transition from one of these two to the other can occur or not remains to be proved. I am sure I have seen it happen.

NEURODERMATITIS CIRCUMSCRIPTA AND ATOPIC DERMATITIS

The "pairing" of neurodermatitis circumscripta and atopic dermatitis should not startle anyone, for I might have labeled them "neurodermatitis circumscripta and neurodermatitis disseminata" instead. Many dermatologists, psychiatrists, pediatricians, and even a few allergists will admit that as the child with persistent atopic dermatitis grows older the appropriateness of the term "neurodermatitis disseminata" increases. Certainly the physical appearance, the course, and the character of the itching of chronic atopic dermatitis may be virtually indistinguishable from that of classic lichen simplex chronicus (lichen Vidal). Whether this is true transition from one "disease" to another or not, and, if so, at what point it may be said to have occurred, must be left to individual judgments.

Attention is invited, however, to the fact that by taking a small step from psoriasis to circumscribed neurodermatitis, and another small step from the latter to atopic dermatitis, we have now gone an almost astronomic distance. The resemblance between typical psoriasis and typical atopic dermatitis is faint, indeed.

ACUTE EXUDATIVE NEURODERMATITIS; EXFOLIATIVE DERMATITIS

Kreibich's acute exudative neurodermatitis and the familiar exfoliative dermatitis do not "pair" particularly well with others. They are inserted into the diagram at this point because the one seems primarily psychogenic and the other is a generalized disturbance of the entire integument and probably of the reticuloendothelial system as well, which may be an ultimate consequence of many of the other disturbances, including psoriasis and some of the multiform erythemas.

PSORIASIS AND SEBORRHEIC DERMATITIS

The physical resemblance between some cases of psoriasis and some cases of seborrheic dermatitis is of course impressive; it not infrequently leads to real difficulty in deciding which diagnosis is more nearly correct in a particular case. In my own experience, it has led to the conviction that a patient may have seborrheic dermatitis at one time and psoriasis at another, or vice versa. This is based, however, on clinical criteria and responsiveness to treatment, and not on histologic or mycologic evidence.

It may be objected that seborrheic dermatitis is widely believed to be a superficial fungus infection, caused by a specific organism, Pityrosporum ovale. Yet there is equally impressive evidence for the aggravation of seborrheic dermatitis (if not its actual causation) by emotional tension, and, more recently, by a specific antagonist of pyridoxine, topically applied; in the latter connection the long-known usefulness of vitamin B complex in treatment is probably significant.

It is also difficult, if one wishes to defend the solely mycologic explanation of the disease, to explain the rarity of contagion and the apparent impossibility of cure. Fungus infections, especially such superficial ones as this, should be curable, not merely controllable. All things considered, it seems unsound to separate seborrheic dermatitis absolutely from psoriasis on this basis, or, indeed, on any other basis. And yet, the comparative ease with which seborrheic dermatitis may be controlled by treatment as compared with the stubbornness of psoriasis demands separation of the two diseases in practice.

In this connection, it is of interest to recall the sharp distinction made a century ago between psoriasis and "lepra vulgaris," which we now realize was merely one of its commoner morphologic variants.

SEBORRHEIC DERMATITIS AND ATOPIC DERMATITIS

How many of us have not puzzled over an infant and finally decided either that the child was suffering from both seborrheic dermatitis and atopic dermatitis, or that only time and the response to treatment would enable us to decide which of the two diseases was present or predominant? And have not many of us seen one of the two gradually give way to the other? In older patients the distinction is rarely a problem, but in young ones it is a very real one, and this seems reasonable justification for pairing seborrheic dermatitis and atopic dermatitis. Still, the justification for regarding them as distinct entities seems too obvious to require elaboration.

SEBORRHEIC DERMATITIS AND DERMATOPHYTOSIS OF THE PALMS AND SOLES

For the grouping together of seborrheic dermatitis and dermatophytosis of the palms and soles the justification is less obvious than I trust it has seemed heretofore. Possibly it is not as sound, either. Here there is little if any physical resemblance. It is rather a question of two fungus infections, both superficial, both virtually noncontagious, both virtually incurable, despite being comparatively responsive to external fungicidal treatment, and both regarded by some observers as capable of being significantly aggravated by emotional tension. These are curious features, if one accepts them as true, for diseases which are primarily fungus infections. Perhaps the fungus element is only part of the story in dermatophytosis, as it appears to be in seborrheic dermatitis.

DERMATOPHYTOSIS AND POMPHOLYX (OR DYSHIDROSIS)

Mimicry of either of the disorders, dermatophytosis and pompholyx, by the other is familiar to all. Indeed, the palmar or plantar dermatophytid may probably properly be regarded as one specific variant of pompholyx. Of course, the occurrence of demonstrable pathogenic fungi in the lesions of dermatophytosis may be regarded as a decisive point, but is it really decisive? Is mycelium always demonstrable in such lesions? Is it never demonstrable in the lesions of pompholyx? Is it the sole etiologic factor in "tinea" of the feet? If so, is the organism really ineradicable, and does it alone explain the incurability of the disease? And if this is true, how are we then to account for the prolonged remissions which may occur? It may be argued that the patient's degree of allergic hypersensitivity to the fungus fluctuates over a period of time, but is such an explanation meaningful, in the light of how little we know of fungus hypersensitivity? It hardly seems sufficient, at any rate, to entirely negate the hypothesis that stress is a factor to be reckoned with here.

What of the pitting of the nail plates, with or without subungual thickening, which is sometimes said to be so characteristic of onychomycosis and which is also said to be so characteristic of psoriasis? Does it differ in any way from the pitting seen in cases of pustular bacterid with nail-matrix involvement or the pitting seen in some cases of rheumatoid arthritis without skin lesions? It seems to me that it does not. And so, perhaps, we can again complete a circle and return to psoriasis again by way of pompholyx and the pustular bacterid.

FIXED DRUG ERUPTION

Fixed drug eruption, an unusual member of the group, does not pair well with any of the others. Limited as to cause (to a specific list of drugs), it still has one feature in common with the pustular bacterid, namely, the characteristic of recurring repeatedly in the same or a slightly larger oval area each time. It is included in the diagram, despite its failure to "fit" into the pattern, largely to arouse critical comment and to stimulate further thought along these lines of integration and correlation.

LICHEN PLANUS

Lichen planus is another disorder that does not pair well with the others. Having a bullous variant as it does, it might be paired with dermatitis herpetiformis, but this bullous variant is so rare that the comparison seems unfair. It shares with psoriasis the capacity for appearing along a scratch mark or at sites of milder trauma. It may closely resemble, especially in its hypertrophic form, circumscribed neurodermatitis. It shares with lupus erythematosus the phenomena of hydropic degeneration of basal cells of the epidermis and absence of parakeratosis, and there is sometimes difficulty in distinguishing clinically between these two diseases, when the pattern described by Crocker as lichen planus erythematosus occurs.

This comparison might well have led, had empirical considerations not already done so, to the treatment of lichen planus with bismuth or gold injections. It has led, more recently, to some trials of corticotropin and cortisone therapy by me and by others. The fundamental importance of psychiatric considerations is of course recognized by most dermatologists.

DERMATITIS REPENS

In dermatitis repens we have the interesting example of a dermatosis (it might have been paired with pompholyx for our purposes) which is remotely related to a very different disease, dermatitis herpetiformis, through one or two intermediary steps in the diagram, which may respond very well to the same treatment which is often so useful in this remote relative, namely, sulfonamides, especially sulfapyridine, by mouth.

VITILIGO AND ALOPECIA AREATA

Vitiligo and alopecia areata, long paired with one another by reason of their not infrequent simultaneous or at least successive occurrence, should probably be included in the chart somewhere. Barber has labeled alopecia areata a stress disorder, and Rothman has recently described effective treatment of it with orally administered cortisone.

COMMENT

The documentation, from the literature and personal experience, of even a part of these impressions, half-formed conclusions, and suggestions would require a book. Even then, it would probably be regarded as inconclusive except by those whose own experience had already led them to the same conclusions. There has been no intention here to try to prove anything, but rather to suggest a way of regarding these puzzling diseases which may make some of the things we know about them seem a little less mysterious.

If the dermatologist regards these diseases in this way, as different-looking, different-acting, differently responding and often differently caused facets of the same fundamental sort of disease process, he will be less inclined to complicate the picture by further elaborations of nomenclature, such as "Stevens-Johnson syndrome," "Libman-Sacks syndrome," or "acrodermatitis pustulosa perstans." He may be helped, too, by being led to apply treatments successful in one member of the group to adjacent members, such as intramuscularly injected bismuth subsalicylate, for example, in nodular vasculitis, or intradermally injected Staphylococcus toxoid, perhaps, in psoriasis. He will be able to keep aloof from the familiar allergic-versus-psychogenic argument that has plagued us so long.

Thus the view has some practical value, different for each physician, no doubt, as a guide in practice and in teaching. More important, I hope, may be its possible value as a starting point for further and more logical and better founded efforts at integration of these diseases. As it stands it is incomplete and in part illogical; I hope it may stimulate others to alter it, reduce it, and probably expand it.

SUMMARY

It is suggested that it is true of these "stress dermatoses," as Osler, in 1900, said of the diseases of the "erythema group," that (*1*) "similarity of lesions may result from a variety of causes," and (*2*) "unity of cause may be associated with a variety of lesions." It is further suggested that many of these dermatoses, which have been attributed to either allergic reactions or emotional tension, or both, may with profit be regarded as being variants of the stress response of Selye. Whether the wide variations in the response are due (*1*) to qualitative variations in the effect of the stressor agent, or (*2*) effects of the actual or apparent etiologic agent independent of its stressor effect, or (*3*) latent innate tendencies or individual predilections of the patient, or any two, or all three, or other as yet unknown factors, remains to be elucidated.

It is pointed out that these dermatoses manifest many curious features in common, such as physical and physiologic resemblances to one another; transitions from one to another; multiple, simultaneous, or consecutive occurrence; and similar therapeutic responsiveness, which are more easily understood if they are regarded as being related to one another.

It is hoped that this way of looking at these diseases may facilitate their management, simplify their diagnosis, clarify their teaching, and perhaps in some instances point the way to a better understanding of their fundamental nature, and, in particular, that it may give pause to the arguments between proponents of their allergic and of their psychogenic nature.

The only new feature of this presentation is the suggested arrangement of these diseases in a mosaic of hexagonal cells which permits similar dermatoses to be set adjacent to one another and thus indicates, in a general way, the integration of the group as a whole and the situations in which similarities and transitions may be found. It is hoped that this form of presentation may be found useful enough so that it will be modified and improved upon by others.

PHYSIOLOGIC STUDIES IN ATOPIC DERMATITIS (DISSEMINATED NEURODERMATITIS)

I. The Local Cutaneous Response to Intradermally Injected Acetylcholine and Epinephrine

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CLINICAL and experimental data are available attesting to the validity of various etiologic concepts of atopic dermatitis, ranging from the pure "allergic" to the pure "psychosomatic." [1] Additional factors such as skin warmth and flare, the sweat retention syndrome, the dry skin component, and the general cutaneous vasospasm, as manifested by pallor and white dermographia, are conditions which are significant in the understanding of the disease. The present series of physiologic studies is being undertaken in an attempt to better understand the etiologic mechanisms involved in the production of this syndrome.

This report will deal with one investigation of the cutaneous vasomotor and sweat gland activity in patients with atopic dermatitis. It was undertaken in an

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attempt to understand the general cutaneous vasospasm as manifested by general pallor as well as the white dermographia ("white line") that results from firm stroking of the skin with a pointed (blunt) instrument.

When the skin of the normal person is firmly stroked with a pointed instrument, the triple response (1. red line, 2. flare, 3. wheal) of Lewis and Grant [2] results. The "red line" (or red reaction) develops in 3 to 15 seconds, is limited to the line of stroke, is due to direct dilatation of the capillaries, and is not dependent upon nervous mechanisms for its occurrence. The "flare" (or spreading flush) develops in a few seconds after the red line, is due to an axon-reflex dilatation of the arterioles, and is dependent upon local nervous mechanisms (axon reflex). The "wheal" (or local edema) is preceded by and completely replaces the red line (red reaction), develops in one to three minutes after injury, is surrounded by the flare, and is due to transudation of fluid from the minute vessels (capillaries) involved previously in the production of the red line (red reaction). Lewis presents evidence that a diffusible H substance (or histamine), thought to be liberated from the injured cells of the epidermis, is responsible for the three reactions comprising the response. There is also some evidence, however, indicating that acetylcholine is responsible for the arteriolar dilatation characteristic of the axon-reflex flare.[3]

When the skin of the patient with atopic dermatitis is stroked with a pointed (dull) instrument, the red line of the first stage of triple response of Lewis and Grant appears in the usual 15 seconds; but then 5 to 15 seconds later (15 to 30 seconds after stroking) vasoconstriction occurs, producing a blanch that replaces the red line, thus producing the well-known white line or "white dermographism." This blanching persists for 2 to 5 minutes and does not have any whealing component. Occasionally a red flare will also be present around this white line. Whitfield [4] has observed the "white line" to light touch and moderate pressure in several different clinical skin lesions. The type stimulus that he applied, however, is not like the heavy stroking under discussion here for the production of "white line."

Some phases of cutaneous vascular physiology of the atopic patient have been studied by Williams [5] and more recently by Eyster, Roth, and Kierland.[6] Williams has shown that the intramuscular administration of histamine to patients with atopic dermatitis produces a greater increase of skin temperature at the sites of predilection for this disease than was produced in his control group of normal persons. Eyster and associates found that the flare portion of the triple response was lacking when 0.1 cc. of a 1 : 100,000 solution of histamine was injected intradermally into patients with the disease.

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It is also important in studying cutaneous vascular physiology to know what will be the vascular response to adrenergic stimuli (example: epinephrine) and to cholinergic stimuli (example: acetylcholine).

When epinephrine (1:10,000 and 1:100,000) is introduced intradermally into normal skin, there is an immediate blanching (vasoconstriction) in the injection wheal due to the direct constrictor (motor) action of epinephrine on the cutaneous blood vessels. This blanching then spreads peripherally with the direct spread of epinephrine, even producing macular (not associated with whealing) white pseudopods of vasoconstriction as the spread of epinephrine occurs via the lymphatics. There is usually an immediate axon-reflex type of flare surrounding this central zone of blanch, which gradually subsides in the usual manner. Recently it has been shown that such intradermally-injected epinephrine will produce moderate sweating in man.[7] This sweating appears in about three minutes after the injection and is localized to the area of blanch (vasoconstriction). Adrenergic blocking agents, such as ergotamine and dibenzyl betachlorethylamine hydrochloride (dibenamine), can inhibit this vasoconstriction and sweating produced by epinephrine.

In contrast to the vasoconstrictor response of epinephrine is the vasodilator response of acetylcholine. When acetylcholine (1:10,000 and 1:100,000) is introduced into the skin of normal persons, two pharmacological effects take place to produce redness (vasodilation) in or around the injection site.[8] The fast, immediate response is the flare. This develops in 5 to 10 seconds as a halo of arteriolar dilatation about the injection site and is of short duration (approximately three minutes). It is identical in appearance to the flare of the triple response and is also the result of an axon reflex, as are the presence of sweating and goose flesh (pilomotion) that occur in this zone of flare. As in any axon reflex, these effects can be blocked by paralyzing the cutaneous nerves with a local anesthetic such as procaine. Atropine, which can inhibit the direct action of acetylcholine, has no effect on these axon-reflex responses (flare, sweating, goose flesh).

The second type of pharmacological effect that takes place in the normal skin when acetylcholine is introduced intradermally is a slow, more prolonged redness that results from a direct (inhibitor?) action of the drug itself on the cutaneous blood vessels to produce a local vasodilation at the injection site. Sweating will also occur due to direct action of the drug on the sweat gland in the same area. This slow longer-acting response will increase in diameter as the acetylcholine diffuses laterally from the injection site. Since this is a direct action, not mediated by cutaneous nerves, procaine has no effect on it. However, atropine will inhibit such vasodilator and sweat gland response to acetylcholine (and physostigmine will enhance them by, in turn, inhibiting the destruction of acetylcholine by cholinesterase).

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8. Coon, J. M., and Rothman, S.: Axon Reflex Responses to Acetylcholine in the Skin, J. Invest. Dermat. **3**:79-97, 1940.

METHOD

This report deals with similar types of observations on the local skin reaction of 10 patients with atopic dermatitis (seven women, three men) who have had acetylcholine and epinephrine introduced into their skin by intradermal injection. A total of 123 experiments were carried out on this group. Acetylcholine was used in dilutions of 1 : 10,000 and 1 : 100,000. Epinephrine was also used in dilutions of 1 : 10,000 and 1 : 100,000. The diluent used was isotonic saline. Each was introduced intradermally with a 26-gauge needle. The amount injected was 0.1 cc. Injections of a similar amount of isotonic saline were used as controls in adjacent areas of skin.

The areas tested were the flexor surfaces of the arms and forearms, the antecubital spaces, and the skin of the back. The tests were placed both in areas of dermatitis and in areas of normal-appearing skin. All sites tested presented the "white-line" response to firm stroking with a pointed instrument. Observations of the local injection sites and adjacent skin areas were made continuously for a minimum of 15 minutes. Recordings of the observations and imprints of the local sweat responses (Randall's technique [9]) were made at 1, 3, 5, 10, and 15, minutes after the

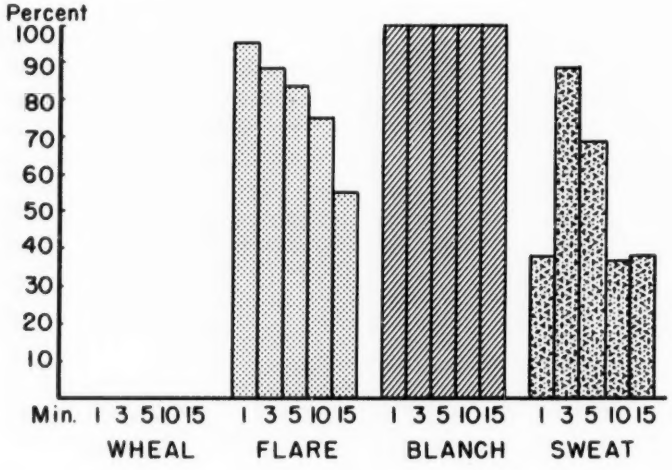

Fig. 1.—Percentage of occurrence of the cutaneous responses, according to the time of appearance, of "atopic persons" to 0.1 cc. intradermal epinephrine (1 : 10,000 and 1 : 100,000).

injection. Attention was focused on the presence or absence of whealing (over 1 cm. in diameter), red flare (axon-reflex vasodilation), blanching (vasoconstriction), the spread of blanching beyond the injection wheal, and sweating. If blanching did not extend beyond the injection wheal, it was not considered significant. At times it was difficult to interpret the presence of red flare in areas of erythematous dermatitis, but, other than this, the response of the abnormal-appearing skin was the same as that of normal-appearing skin to either acetylcholine or epinephrine in these atopic persons. Accordingly, then, the data of abnormal and normal-appearing skin will be grouped together. There was no marked difference in the responses elicited from the two concentrations used for each drug (1 : 10,000 and 1 : 100,000).

9. Randall, W. C.: Quantitative and Regional Distribution of Sweat Glands in Man, J. Clin. Invest. **25**:761-767, 1946.

TABLE 1.—*Atopic Persons; Intradermal Epinephrine (1: 10,000 and 1: 100,000)*

Time After Injection	Wheal			Flare			Blanch			Sweat		
	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence
1 min.	0	26	0	25	26	96	26	26	100	10	26	38
3 min.	0	29	0	26	29	89	29	29	100	26	29	89
5 min.	0	29	0	24	29	83	29	29	100	20	29	69
10 min.	0	24	0	18	24	75	24	24	100	9	24	37
15 min.	0	18	0	10	18	55	18	18	100	7	18	38

Fig. 2.—Sweat imprint pattern (Randall's technique) three minutes after the intradermal injection of 0.1 cc. epinephrine (1 : 100,000) in the skin of an "atopic person." Each black dot represents a sweat droplet discharged from one sweat pore.

RESULTS

Epinephrine (Table 1, Fig. 1).—The responses of the skin of these atopic persons to the injection of epinephrine are the same qualitatively and quantitatively as those seen in normal persons. No whealing was observed. Red flare (axon reflex) was observed in 96% of the tests at the end of one minute and then gradually began to fade in size, intensity, and incidence, so that it was present in only one-half the tests at the end of 15 minutes. Blanch (vasoconstriction) was present in 100% of all the observations and increased in size during the entire experiment, developing macular (not associated with whealing) white pseudopods

of vasoconstriction as the spread of the epinephrine occurred via the lymphatics. Sweating occurred in moderate amounts (Fig. 2) in 38% of the observations at the end of 1 minute, in 89% at the end of 3 minutes, and then gradually subsided in occurrence and amount so that there was only a 38% incidence at the 15-minute observation period. This moderate sweat response, beginning in approximately three minutes after intradermally injected epinephrine in the atopic patient, coincides in incidence, severity, and time of occurrence with recent reports of sweating on the normal human skin from similarly injected epinephrine.[7] It must be emphasized that although there seems to be no doubt that the sweat glands respond directly to epinephrine, it is felt that the existence and function of an adrenergic innervation of human accrine sweat glands is not yet proved.[10]

Acetylcholine (Table 2, Fig. 3).—Some of the local skin responses to the intradermal injections of the acetylcholine observed in the atopic person were the same as are seen in normal persons, i. e., the "flare" and the "sweat response."[8] The incidence of "whealing" may be a little higher than one would be led to expect from previous reports.[11] The marked variance from normal was observed in the "delayed blanch" phenomenon, which slowly spread beyond the injection wheal.

TABLE 2.—*Atopic Persons; Intradermal Acetylcholine (1: 10,000 and 1: 100,000)*

Time After Injection	Wheal			Flare			Delayed Blanch			Sweat		
	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence	Incidence	Total Observations	% Occurrence
1 min.	8	39	20	36	39	92	8	39	20	39	39	100
3 min.	12	34	35	31	34	91	27	34	79	33	33	100
5 min.	17	37	46	31	37	83	37	37	100	36	37	98
10 min.	8	35	22	30	35	85	35	35	100	29	35	82
15 min.	5	34	14	19	34	55	34	34	100	19	34	55

Whealing of more than 1 cm. in diameter occurred at 1 minute in 20% of the tests, at 3 minutes in 35%, at 5 minutes in 46%, and then dropped off in incidence to 22% and 14%, respectively, at 10 and 15 minutes.

Flare (axon-reflex vasodilation) of the arterioles occurred immediately after injection in all normal-appearing skin, but it was difficult to interpret in some inflamed areas. Flare then decreased in intensity, width, and incidence, so that it was only visible in 55% of the test sites at 15 minutes, and even when present, only a small residual remained. This flare response is the same as the flare to acetylcholine in normal persons.

As indicated above, the only deviation from the normal cutaneous vascular response occurred as a "delayed blanch" (vasoconstriction) after the injection of acetylcholine (Fig. 4). This "delayed blanch" could be seen on the wheal and just beyond it in 20% of the tests at the end of one minute. This vasoconstriction (spreading peripherally and encroaching on the flare from within) then increased in size, intensity, and incidence throughout the entire observation period. At the

10. Lobitz, W. C., Jr.: Recent Developments in the Physiology of the Sweat Apparatus, A. M. A. Arch. Dermat. & Syph. **66**:152-155, 1952.

11. Hopkins, J. G.; Kesten, B. M., and Hazel, O. G.: Urticaria Provoked by Heat or by Psychic Stimuli, Arch. Dermat. & Syph. **38**:679-691, 1938.

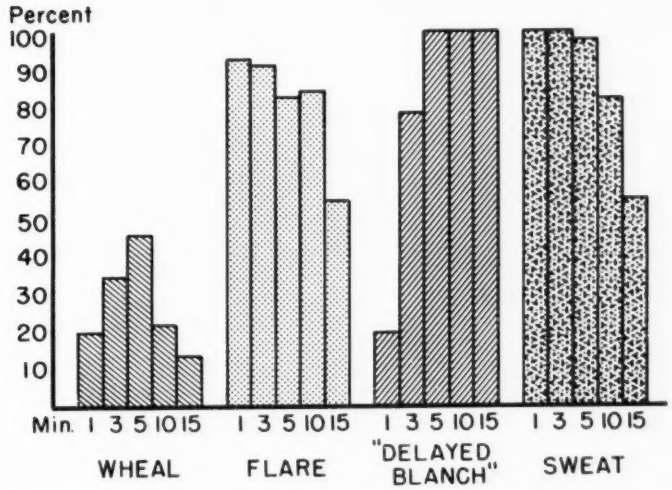

Fig. 3.—Percentage of occurrence of the cutaneous responses, according to the time of appearance, of the "atopic person" to 0.1 cc. intradermal acetylcholine (1 : 10,000 and 1 : 100,000).

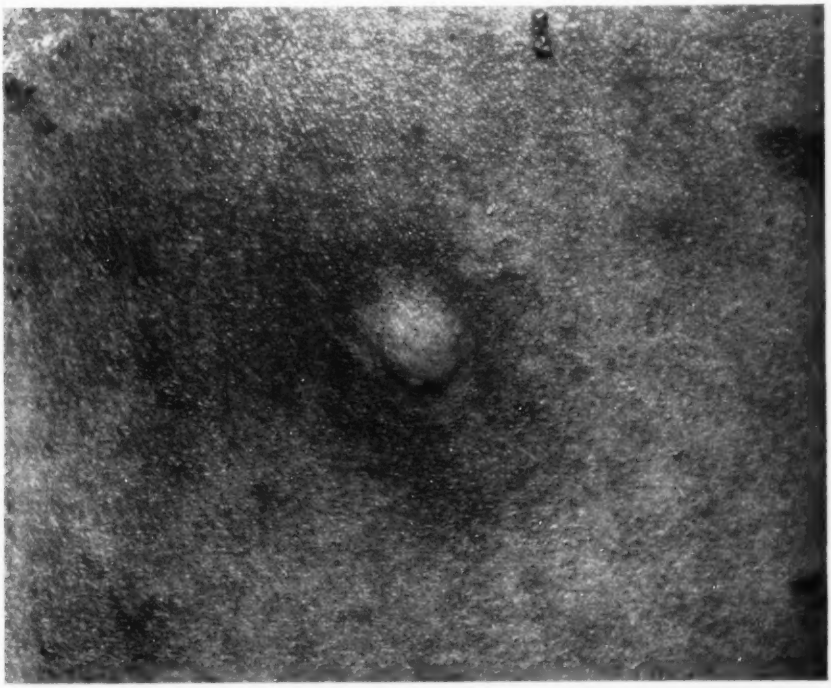

Fig. 4.—Photograph of the cutaneous response five minutes after the intradermal injection of acetylcholine (1 : 10,000) into the normal-appearing skin of an "atopic person." Note the central wheal, the "delayed blanch" spreading beyond the wheal with pseudopods of vasconstriction, and the "flare."

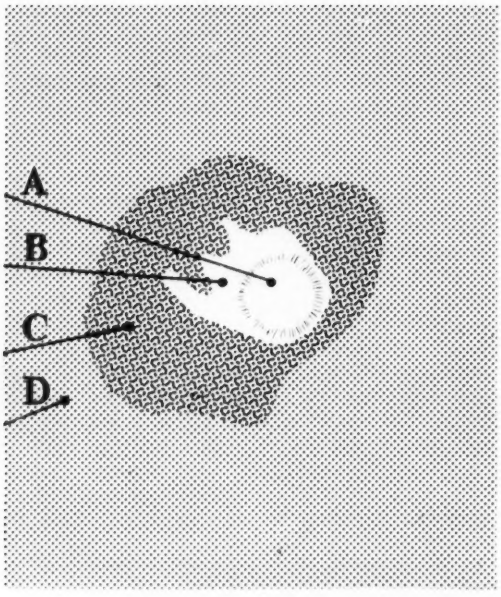

Fig. 5.—A diagrammatic representation of Figure 4. *A*, raised wheal; *B*, "delayed blanch"; *C*, red flare; *D*, normal skin.

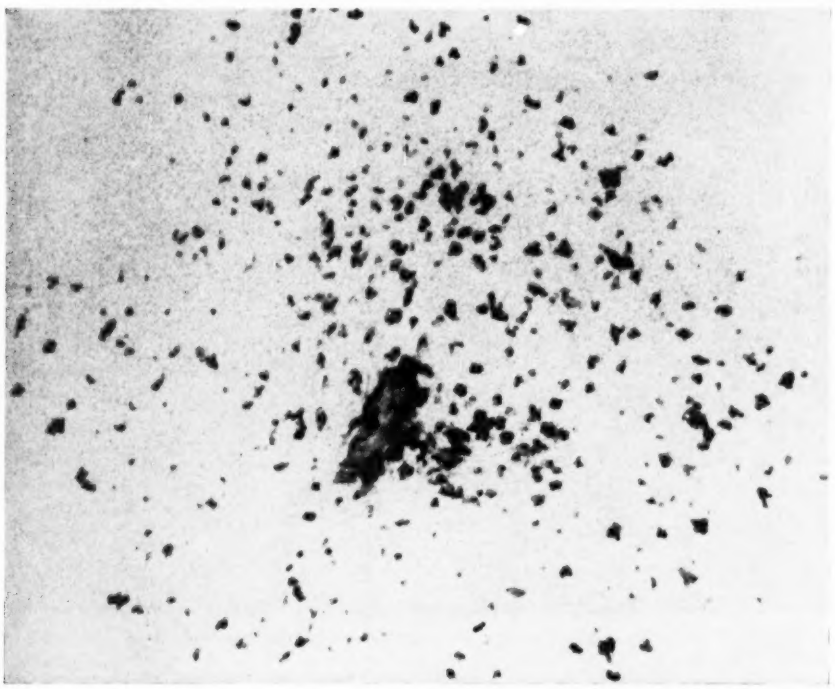

Fig. 6.—Sweat imprint pattern (Randall's technique) three minutes after the intradermal injection of 0.1 cc. acetylcholine (1:10,000) into the skin of an "atopic person." Each black dot represents a sweat droplet discharged from one sweat pore.

5-, 10-, and 15-minute observation periods, all test sites (100%) revealed this phenomenon. Spread of "delayed blanch," like that seen with epinephrine with macular white pseudopods of vasoconstriction not associated with whealing, was reminiscent of a lymphatic spread of a vasoconstricting substance. This blanching was seen to persist for over 60 minutes in two patients, although the usual duration was between 15 and 30 minutes. The adjacent skin sites did not show this "delayed blanch" phenomenon after injections with isotonic saline as controls, nor after similar injections with distilled water. This "delayed blanch" phenomenon, developing at 3 to 5 minutes and slowly spreading peripherally beyond the injection site and of 15 to 30 minutes' duration, is not to be confused with the "white reaction" (blanch) that is seen when the skin of the atopic person is firmly stroked with a pointed instrument. The latter reaction to trauma is also seen on the local injection wheal of the saline controls; it differs, however, from the "delayed blanch" in that it develops 15 to 30 seconds after the injection, is localized to the injection site, and is of two to five minutes' average duration.[4]

The sweat response to the acetylcholine was like that of normal persons (Fig. 5), occurring both as a fast onset axon-reflex response in the flare area and as a slow prolonged direct action response in the injection area.[5] It occurred in 100% of the tests in the first three minutes. The slow direct action type of sweating continued even in the developing area of "delayed blanch," but the amount and incidence of sweating gradually decreased with time (55% at 15 minutes).

COMMENT

As indicated above, the striking deviation from the normal of this group of atopic persons in these adrenergic and cholinergic studies was the "delayed blanch" response to acetylcholine injections. It is not possible as yet to explain this paradoxical response of vasoconstriction from such intradermally-injected acetylcholine. Studies are in progress to try to explain the mechanism of this phenomenon. Although enough data have not yet been gathered in this regard, some preliminary observations and postulations might be of interest.

There seems to be a critical level of acetylcholine concentration necessary to produce the "delayed blanch." When intradermal tests were carried out with acetylcholine diluted from 1 : 100 to 1 : 1,000,000,000, the delayed blanch phenomenon persisted up through a 1 : 1,000,000 dilution, but did not develop with a 1 : 10,000,000 dilution or weaker.

Acetylcholine is quickly destroyed by cholinesterase in the skin and the time of the development of the "delayed blanch" at three to five minutes might coincide with this destruction. However, to date the longer-acting cholinergic drugs, such as methacholine (Mecholy) and carbachol (Doryl) also produce exactly the same "delayed blanch" (vasoconstriction) phenomenon in these atopic persons.

As mentioned above, two pharmacological effects take place when acetylcholine is introduced intradermally into the skin of normal persons. The fast, short-lived axon reflex can be blocked by paralyzing the cutaneous nerves with intradermally-injected procaine. To date we have been unable to effect the development and progress of the "delayed-blanch" phenomenon with such intradermally-injected procaine, even though such injections did block the development of the axon-reflex

flare and axon-reflex sweating. This failure of procaine to affect the "delayed blanch" plus the time factors involved (quick axon-reflex flare versus a slow "delayed blanch") indicate that this vasoconstricting response is not due to an axon reflex.

The slower, longer-lived response resulting from a direct action of the acetylcholine that cannot be affected by procaine can, however, be blocked with atropine. To date, we have been able to block successfully this "delayed-blanch" phenomenon in the skin site of atopic persons who have been previously injected with atropine sulfate (1:1,000, 1:10,000, and 1:100,000) intradermally 2 or 24 hours before the acetylcholine injections.

The slowness of onset of the "delayed blanch" (three to five minutes), the slowness of its spread peripherally, and the lymphatic-like type of spread making pseudopods of vasoconstriction not associated with whealing would also suggest that the phenomenon was the result of the direct action of the vasoconstrictor substance on the blood vessels of the skin.

One must suppose that such a vasoconstrictor substance is either (1) acetylcholine itself acting to give a motor response (constrictor) rather than the usual inhibitor response (dilator), or (2) some other vasoconstricting substance which is being released after acetylcholine has been injected. To our knowledge, there is no precedent in the literature for the latter supposition.

There is precedence in the literature for the former, i. e., acetylcholine can produce a motor (constrictor) response. Burn [12] presents evidence that acetylcholine plays a role in regulating tissue activity locally. When normal concentrations of acetylcholine are present in the smooth muscle of blood vessels (isolated rabbit-ear preparation), additional acetylcholine will exert an inhibitor effect (dilator). However, if the acetylcholine normally present is leeched out of the vessels by long, continued perfusion so that this tissue is deficient in acetylcholine, the addition of more acetylcholine will no longer produce an inhibitor (dilator) response, but will produce a motor response (vasoconstriction).

Studies designed to evaluate the autonomic nervous system responses of these atopic persons are in progress, not only with reference to their skin, but also with reference to the visceral functions.

SUMMARY

The cutaneous vasomotor and sweat gland responses to intradermally-injected acetylcholine and epinephrine in patients with atopic dermatitis are described.

The response to epinephrine is the same as that which is described for normal persons, including the production of moderate sweating in the vasoconstrictor zone.

The sweat response and axon-reflex response to acetylcholine are normal. However, a marked deviation from normal occurs as evidenced by the development of a "delayed blanch" (vasoconstriction) beyond the injection wheal that occurs between three and five minutes after the intradermal injection. The possible mechanisms of this unusual response are discussed.

12. Burn, J. H.: Relation of Motor and Inhibitor Effects of Local Hormones, Physiol. Rev. **30**:177-193, 1950.

ABSTRACT OF DISCUSSION

OF PAPERS BY DR. HARRY L. ARNOLD JR. AND DR. WALTER C. LOBITZ JR.

DR. MAXIMILLAN OBERMAYER, Los Angeles: The two studies of Dr. Arnold and Dr. Lobitz represent two completely different approaches to the etiologic riddle of those common inflammatory dermatoses in which psychosomatic and allergic factors are operative in varying degree. Because so many different methods have been used to solve this riddle it might be well to review them all, so as to see how these two studies integrate with the whole.

The methods of research may be grouped into five categories: psychologic, neurophysiologic, biochemical, allergic, and speculative or philosophic.

The simplest of the psychologic procedures, used by most of us, consists of the correlation of psychiatric and dermatologic data obtained from the history. This lacks preciseness. A more thorough method is by clinical psychiatric study. The validity of this method depends on the qualifications of the observers, who are workers with widely varying spheres of experience. Projective techniques have the advantage of greater objectivity, but the correct interpretation of the test material is again dependent on the qualifications of the interpreter. Hypnosis is a promising tool, as was shown by Seitz. Psychoanalysis, the most penetrating and trustworthy method, is necessarily confined to a very small amount of material.

Neurophysiologic research has taken several directions such as basic studies on the function of the hypothalamic centers, encephalography, response to stress (of intense interest at the present time), and testing cutaneous function. The function of the skin has been investigated by studies of temperature, the reactive hyperemia threshold, the threshold of pain, reactions of the skin to epinephrine, histamine, acetylcholine, and pilocarpine, palmar resistance, sweat, and exudation; these studies have been widely pursued not only because they are a promising field but because they satisfy the natural desire of the scientifically minded worker for measurable data.

Few biochemical studies have been made aside from those on the pH of the skin and Engman's work on magnesium deficiency in neurodermatitis.

The purely allergic method has not been promising, as has been increasingly realized.

Among the speculative attempts are three of interest: The influence of the climate concerning which we shall soon hear a new contribution; the concept of neurocirculatory instability or protoplasmatic unrest of Becker, and, now, Arnold's hypothesis of the inherent reaction patterns.

With the growing realization that not one of these five approaches to the problem has been adequate, the trend is toward combining them. Examples of constructive effort are correlation of psychologic methods with one another, of psychologic methods with neurophysiologic, especially cutaneous function; of neurophysiologic methods with one another, particularly response to stress, and cutaneous function.

Dr. Arnold's work, then, represents a speculative or philosophic study based on a neurophysiologic concept. This is reminiscent of Becker's idea of neurocirculatory instability based, more speculatively, on the concept of protoplasmatic unrest. Both hypotheses are all-embracing.

There is some reason for accepting the inclusion of the dermatoses grouped together by Arnold among Selye's diseases of adaptation. Sternberg and Zimmerman's studies on the response to stress of patients with neurodermatitis have shown results which may be significant.

Granted the validity of the speculative basis, Arnold has led us to visualize the interrelationship of the various dermatoses, beginning and ending with psoriasis, coming full-circle like the characters in Schnitzler's play "La Ronde." That interrelation is best exemplified by their temporary suppression with corticotropin (ACTH) or cortisone in all of them. The other factors of alleged relationship are far more tenuous, yet sufficient to make us doubt the rationale of our labels bestowed on some of the dermatoses. The observation of transitions, especially in neurodermatitis, psoriasis, and seborrheic dermatitis, I corroborate from my own experience. Yet, the idea comes to mind that the apparent similarities may not be due to a common fundamental cause but rather to the relatively few ways in which tissues can respond, both clinically and histo-

pathologically, to any stimulus, whether an actually causal one, a releasing agent, or a therapeutic measure. Moreover, Arnold's hypothesis leaves us with the same bucketful of dermatoses to worry about, even if we accept their interrelations and change our labels. All this does not detract from the inherent worth of a philosophic study like his; it is challenging and thought-provoking. It certainly illustrates the folly of continuing battle between the allergic and the psychosomatic approaches, a point which I expressed in print a decade ago.

Dr. Lobitz' work represents the purely experimental approach. Studies like his are important because they add, stone by painfully laid stone, to a structure which may one day serve as a laboratory for psychoanalysis, a science so badly in need of one.

The propensity of the patient with neurodermatitis to vascular spasms, clinically discernible as pallor, is one of the several traits frequently present in this diathesis. The "delayed blanch" reaction elicited by acetylcholine represents a distinct deviation from the normal. It is possible that further studies along these lines may help to elucidate the whole problem of abnormal response of the autonomic nervous system in these patients and thus perhaps eventually furnish the much-needed answer to the neurophysiologic mechanism involved in the somatic expression of an emotional stimulus.

Dr. Marion B. Sulzberger, New York: The Association is to be congratulated on the presentation which we have been permitted to hear from Dr. Lobitz, and I must express also my admiration of Dr. Arnold's presentation. The mosaic which he has drawn of these various dermatoses is simply an illustration of the thesis that if you rely entirely upon more or less superficial resemblances, you can link almost any disease to almost any other disease through atypical cases and *faites de passages*, i. e., transitional forms and combined forms. For instance, I do not see why one could not just as well have included in Dr. Arnold's mosaic of hexagons transitions from such diseases as impetigo to impetigo herpetiformis, or from impetigo to Kaposi's varicelliform eruption, or from fungous infections to eczematous dermatitis.

As far as I can see, the only reason why impetigo and fungous infections and virus infections are left out is not because of their lack of clinical resemblance to the other members, but because these are diseases of which we happen to know the etiologic causes.

The second point is, moreover, if one wishes to assume the existence of fundamental relationships on the basis of mere resemblance, one could draw lines and point to similarities in etiologically very different internal diseases—in pulmonary diseases, for example, between tuberculosis and sarcoids of the lungs, and between these and moniliasis of the lungs and coccidiomycotic and blastomycotic infections of the lungs. These have just as many resemblances to each other as have the skin diseases in mosaic which Dr. Arnold has presented.

It seems to me that, in order for it to be tenable or valuable for further investigation, any proposition or concept which seeks to explain the causes of a disease or of a group of diseases must necessarily explain and account in some way for the essential characteristics of the pictures or picture concerned. In the evaluation of the concept of the psychiatrists in regard to "psychosomatic" skin diseases, one of the difficulties which I always encounter is that I often fail to recognize exactly what they are talking about when they describe their clinical dermatologic "entities" or groups. There is often no homogeneity in the groups which they present as a unit, and they often throw together what often appears to be a haphazard, motley hodge-podge of many different dermatologic conditions. Very often I cannot understand what they are talking about dermatologically, nor can I even distinguish clearly between the composition of the group which they consider their experimental group and that of the group which they consider their controls. Both groups are often so indistinct and inaccurate in their dermatologic delineation that I cannot for the life of me distinguish between them.

That is not the case here. I understand very well all the entities that Dr. Arnold is talking about and the entity which Dr. Lobitz is talking about, and I shall just select one of them, namely, atopic dermatitis, for further discussion.

I think that in order to explain anything about the causes of atopic dermatitis one must explain the characteristic phenomena which we agree form the essentials of this syndrome. One of the characteristic manifestations of this form of atopy is infantile eczema. Are these atopic

infants at the age of one year or less subjected to entirely different stresses from the other infants? If that is the case, why does the infantile eczema usually clear up before the age of 2 years? How does the chronology of emotional stresses account for this relief in the skin responses? Then one must include hay fever and asthma in this syndrome. Can one explain on the basis of a stress or as a manifestation of an adaptation dermatosis the fact that some people have their attacks in the spring and some in the fall, according to the type of pollen in the air and according to their sensitivity as demonstrable by skin tests and circulating antibodies to the respective pollens?

Can one ascribe on a psychosomatic basis the formula which each of these atopic persons will have in regard to his urticarial reaction to skin tests with several hundred antigens? Can one demonstrate that the individual Prausnitz-Kuestner antibody assortment in the serum in each of these cases could conceivably be a resultant of any psychic constellation? Can one explain the ophthalmic cataracts which occur in these patients on the basis of stress or psychic tensions? These are among the dozens of fundamental differences which characterize the patient with atopic dermatitis. And included among these differences is, as Dr. Lobitz has just now again brought out, the well-known white response to stroking. Clinically we not only get this white mark, this blanching shortly after stroking, but after some delay, a minute or so, we observe that the edges of the white mark become indistinct. The blanched area remains clearly visible for about 1 to 10 minutes or so, and, then, as it diffuses out it disappears. In explaining atopic dermatitis, one must explain not only this white mark and all the previously described characteristics but also the characteristic localizations of these dermatoses, how and why they affect mainly the flexures and the face. And why do they take their characteristic course? Why do they not begin until the second month of life, as a rule? And why do they clear up in two years as a rule in the infant? Why do these so often appear again in children let's say 6, 7, 8, or 9 years old, often clear up again, often reappear in adolescence, and disappear spontaneously at or before the age of 22 in the large majority of cases. Do these people all become free of stress on this sort of regular timetable? Or do they all lose their pathologic response to stress periodically during these clear periods with such regularity and uniformity? That is indeed hard to conceive. Then how can one explain that atopic dermatitis so often gets better in the dry warm climates, as you will soon hear from Dr. Leslie Smith? How can one explain the familial transmission, the genetics of atopic conditions on the basis of psychic stresses? Do you not think that perhaps the answers are much simpler? Perhaps we are not talking about causal agents at all. Whether we talk about psychosomatic effects or about nerves or about the climate or about food or other allergens, perhaps we are never mentioning causes at all but only trigger factors. In all probability all these factors, alone and in combination, are but elicitors of exacerbation of disease and not causal agents or mechanisms. Perhaps the true causes and fundamental mechanisms of atopic disease are somewhere else, somewhere deeper than we know or different from anything we know of today. Well, that is one of the ideas which is implied by what Dr. Lobitz has told us today.

I want to thank both the presenters and discussers for stimulating us to more thought about these very complex and important problems.

Dr. George C. Andrews: I also enjoyed both these papers very much, and I can understand how Dr. Arnold would classify pustular psoriasis as a stress syndrome. There has been a great tendency to confuse pustular bacterid and pustular psoriasis throughout the years. Dr. Barber and I have agreed that they are both distinct entities. We have sent pictures back and forth of the two different diseases, and we think that they are entirely different from one another.

Pustular bacterid was described as a distinct entity, entirely different from pustular psoriasis, and I have never denied existence of the latter in any way. In the diagnosis of bacterid it is a matter of focal infections and reactions to sensitization of bacterial products from focal infection. The condition is curable. If it is not curable by means of removal of the focal infection, I would not call it pustular bacterid although it might be. I would not make a diagnosis of pustular bacterid unless the person has at times also a leucocytosis. By this I mean over 12,000 or 15,000 white blood cells.

We nearly always pick up a leucocytosis in the cases of pustular bacterid, not always I must admit, but nearly always, especially during the outcropping of new lesions. We see that over and over again.

The histology is also quite distinct from that of dermatitis herpetiformis and impetigo and of what is called stress dermatoses. It is the histology of an "id." When pustular psoriasis is present, I do not believe it can be cured by removal of focal infections. That is, when there are definite signs of psoriasis or a history of psoriasis, and, in addition, vesicopustular eruptions of the palms and soles, known as pustular psoriasis of the extremities. I have known of several cases in which attempts have been made to cure, and they have never been successful. However, the frequency with which pustular bacterid is cleared by removal of the focal infections is so great that I think that, without any question, it is a very distinct entity. I think that the two should not be confused.

Dr. Louis A. Brunsting, Rochester, Minn.: In his excellent presentation, Dr. Lobitz has demonstrated that atopic persons are peculiar people; they are peculiar in their reaction in the skin and in the nervous system as well. This latter feature is brought out by the abnormal response of such persons to studies by encephalology. I should like to ask Dr. Lobitz whether he has had occasion to perform his experiments on atopic persons who have had a unilateral sympathetic ganglionectomy.

Dr. Stephen Rothman, Chicago: I wish to congratulate Dr. Lobitz on his admirable work. The paradoxical finding of blanching of the skin by acetylcholine and the spread of this blanching is entirely novel and certainly difficult to explain. To my knowledge, this is the first instance that an abnormal physiological vascular reaction has been demonstrated experimentally in atopic dermatitis.

Dr. Harry L. Arnold Jr.: I should like to thank Dr. Obermayer for his courteous and forbearing treatment of my presentation, and Dr. Sulzberger for his inquiry regarding the reasons for not including herpes simplex and impetigo in the "Talmudic mosaic." I suspect him of having been a little facetious, but I do not think that it was actually a facetious question. These diseases could very well be included in the mosaic, though just where I do not know. The reason for not including them, or other infectious diseases, is simply that in those conditions there is a single specific cause, the micro-organism, which is so much more important than any of the contributory stressor agents that it quite puts them in the shade and renders them unimportant. Moreover, such diseases are specific etiologic entities, for the most part, rather than being capable of being caused by a variety of causative agents, and they do not tend to undergo transition into other disease forms as do most of the disorders in the mosaic.

Dr. Andrews' point about the sharp distinction between pustular psoriasis and the pustular palmar bacterid is not easily answered. I have never been sure that I could distinguish between them, and I still feel that I see an occasional case of atypical psoriasis with palmar lesions that I would call, if they were the sole manifestation of skin trouble, pustular bacterid.

I should like to reemphasize that the entire pattern which I suggest for relating these diseases to one another is a philosophic concept for which I can only hope more cogent biologic evidence may be found in the future. It is a concept which I have found extremely useful in evaluating cases and in teaching interns and residents about this group of diseases.

Dr. Walter C. Lobitz: I wish to thank the discussers; you have been very kind. This "white line" that we see clinically in the atopic person becomes a very valuable sign. We have been impressed with the fact that it will develop (after firm stroking) before the skin of the atopic person goes into an acute flare. On the other hand, it will persist even after the skin has returned to normal. Not until such "white line" is replaced by the normal "triple response" can we consider an atopic person as being completely well. In this presentation, I did not belabor this clinical development of the atopic white line, but it is in detail in the manuscript.

I realize that it is not a good idea to speculate at such a time as this; however, the part played by acetylcholine in the entire physiologic make-up of a person is becoming more clear. Several years ago, Dr. Hopkins, Dr. Hazel, and Dr. Keston indicated the role of acetylcholine in the

production of physical urticaria. The allergists are now becoming interested in acetylcholine mechanisms in their specialty. At the other extreme, the psychiatrists, too, are beginning to talk about cholinergic and adrenergic emotions, emotions that imitate or are associated with the responses to acetylcholine or epinephrine.

Several of us these past few days have been discussing whether perhaps the atopic person might have been born with a defect in acetylcholine metabolism. Broadly speaking, the cholinergic and adrenergic physiologic responses are continually buffering each other for the protection of the normal person. But here is an atopic person who, as far as his skin is concerned, has the same reaction to both stimuli, i. e., intense vasospasm. What is such a situation also doing to the rest of his system? These are things we hope to find out.

Dr. Brunsting's point about the studies in a "sympathectomized" group of persons is extremely important. At the present time, we are collaborating with our neurosurgeons in studying such skin reactions in this group, as well as in patients with peripheral nerve injury and with paraplegia (spinal cord and brain damage).

Histologic studies are in progress. The vascular responses to local (intradermal) injection of histamine are the same in the atopic person as in the normal person.

ERYTHEMA ANNULARE CENTRIFUGUM

Its Relation to Internal Disease

ARTHUR STILLIANS, M.D.
CHICAGO

ERYTHEMA annulare centrifugum, a rare dermatosis, usually occurs in otherwise healthy persons; however, some cases have been reported in which it was associated with internal disease. Because of the possibility of discovering a clue to its etiology, such cases are of especial interest. I wish to record one that I observed for a short time.

REPORT OF A CASE

Mrs. J. S., a 60-year-old white housewife, a native of the United States, had a total hysterectomy and salpingectomy in 1941. The uterus contained fibroids and a hypertrophic endometrium; there were subserous cysts of the Fallopian tubes, and an ovarian fibroid. No sign of carcinoma was found.

Late in 1950 the patient began to suffer from painful swellings of the legs, malaise, and anorexia, with diffuse aching pains followed by swelling of the abdomen. A series of deep x-ray treatments relieved her; the abdominal swelling and edema of the legs subsided, and she was able to get about again.

Early in February, 1951, the abdominal enlargement recurred; malignant cells were found in the ascites fluid, and on Feb. 28 an exploratory operation by Dr. Mark Goldstine, at Wesley Memorial Hospital, revealed extensive carcinomatous metastases throughout the omentum, the peritoneal wall, and all visible viscera. This was confirmed microscopically. After the operation the ascites fluid increased, necessitating frequent tapping.

On March 31 the laboratory examination revealed 13.28 gm. of hemoglobin and 5,900 white blood cells per cubic millimeter, of which 43% were segmented and 7% unsegmented polymorphonuclears, 46% lymphocytes, 2% mononuclears, and 2% eosinophiles. The nonprotein nitrogen count was 23 mg. per 100 cc., serum albumin 2.49 gm., and serum globulin 2.31 mg. The Kahn serum test was negative. The urine contained no albumin or sugar.

On April 30 the patient noticed an eruption with mild itching on the lower abdomen and on both thighs.

When I saw her four days later, most of the eruption was on the outer side of the right thigh. It consisted of 9 or 10 flat papules and nodules from 5 to 10 mm. in diameter, the larger ones showing a tendency to become arcuate. Beside these were four large, rings-shaped figures bordered for the most part by small or large arcs, forming festoons. Their walls were smooth, pale red, about 3 mm. in width and 1 mm. above the general skin surface; they were firm and not tender. The outer side of the wall rose abruptly, but the inner side sloped gradually to the general skin surface. Within the circles the skin was of normal color or slightly brownish.

The largest of these rings was 7 cm. in diameter on May 4, but the next day it had grown to 8 cm. On succeeding days the large lesions faded and the smaller one enlarged and became circinate. As those on the right thigh subsided, the fewer lesions on the left thigh increased in number and in size.

The same rapid evolution, fading, and recurrence of the festooned circles persisted until a few days before the death of the patient on Aug. 15, 1951, about three and one-half months after onset of the eruption.[1]

1. Dr. Garford Harris, who attended the patient at her home, supplied this information.

The excellent papers of Graham and Throne,[2] Wernsdörfer,[3] and others record a number of cases of erythema annulare centrifugum associated with internal disease. Pautrier's patient had a mediastinal tumor and generalized adenopathy.

Hudelo, mentioned by Proppe,[4] reported the case of a patient who had a malignant tumor accompanied by erythema annulare centrifugum.

Appearance of the eruption on May 4, 1951.

2. Graham, T. N., and Throne, B.: Érythème annulaire centrifuge: Report of 6 Cases, Arch. Dermat. & Syph. **22**:777, 1930.

3. Wernsdörfer, R.: Über Erythema annulare centrifugum (Darier) mit Mitteilung zweier selbstbeobachteter Fälle, Arch. Dermat. u. Syph. **182**:41, 1941.

4. Proppe, A.: Über Erytheme, Dermat. Ztschr. **68**:331, 1934.

Gammel [5] has recently reported a case of erythema gyratum migrans, a scaly macular or slightly papular eruption, which in its configuration and rapid changes resembled erythema annulare centrifugum. It occurred in a woman of 56, who on examination was found to have a small carcinoma of the breast. This growth was removed, and six weeks after the operation the generalized skin eruption which had been present for nearly a year cleared up; there has been no recurrence in the ensuing four years.

Butler's [6] patient with typical erythema annulare centrifugum had a heart lesion. Lisi's [7] had chronic arthritis. These two reports bring to mind the description by Keil [8] of erythema rheumaticum marginatum.

Keil writes:

> The dermatosis appeared in the form of circles or segments of circles of varying sizes, occasionally attaining a diameter of several inches. The borders were raised above the level of the surrounding skin, were colored dull red, and were sharply circumscribed; individual papules could not be distinguished in the rampart. The contrasting centers were flat and characteristically colored varying shades of brown, sometimes a more livid hue. When isolated patches developed more rapidly than usual the central area revealed but little discoloration, though this occurrence was relatively uncommon. By peripheral extension and coalescence of contigous rings, polycyclic and geographical figures were produced, resulting in a most bizarre appearance. . . . The eruption was characterized further by sudden onset, rapid spread and transiency of lesions. In several instances the eruption appeared over night and faded in several hours.

Itching was slight, scaling was absent as a rule, and the eruption sometimes faded as the temperature subsided and recurred with a recurrence of fever. Urticarial features were noted sometimes.

Resemblance to the annular dermatosis of Darier seems to me close, though the rheumatic eruption devlops and clears even more rapidly than erythema annulare centrifugum. Also, the fact that the marginate form of erythema rheumaticum is an uncommon variant of the macular form is a distinguishing feature. Both forms are associated with cardiac involvement.

Minor infections have been reported in association with erythema annulare centrifugum by several authors, and shock, antecedent to the outbreak of erythema annulare centrifugum, has been recorded by Wise,[9] in whose patient the skin eruption developed soon after a burn. Shaw [10] reported the onset of erythema annulare centrifugum after the birth of a dead fetus, and Lustgarten,[11] one of the early writers on the subject, considered the kick of a horse an etiologic factor in his case.

It is natural in considering so fluctuating an eruption as erythema annulare centrifugum to think of urticaria. Typical wheals have been seen in several cases of erythema annulare centrifugum, but more frequently vesicles and even bullae have

5. Gammel, J. A.: Erythema Gyratum Migrans, read before the American Dermatological Association, Inc., Colorado Springs, Colo., April 20, 1952.

6. Butler, J.: Erythema Annulare Centrifugum, Arch. Dermat. & Syph. **25**:111, 1932.

7. Lisi, F.: Su di un caso di eritema cronico, recidivante, papuloso e figurato, del tipo "eritema anulare centrifugo di Darier," Gior. ital. dermat. e sif. **77**:421, 1936.

8. Keil, H.: The Rheumatic Erythemas: A Critical Survey, Ann. Int. Med. **11**:2223, 1938.

9. Wise, F.: Erythema Annulare Centrifugum, Arch. Dermat. & Syph. **22**:728, 1930.

10. Shaw, H. C.: Erythema Annulare of Darier, Arch. Dermat. & Syph. **28**:260, 1933.

11. Lustgarten: Erythema Papulatum vel Urticatum Figurans, Perstans et Chronicum, J. Cutan. Dis. **11**:110, 1893.

appeared. The production of vesicles following the administration of potassium iodide has been reported by several observers, suggesting a relation to dermatitis herpetiformis. In Sabouraud's case, cited by Graham and Thorne, eosinophilia and the histological picture pointed to dermatitis herpetiformis.

Hudelo reported that erythema annulare centrifugum in his patient was succeeded seven and one-half months later by dermatitis herpetiformis.

A number of Japanese observers, including Yoshihiro (cited by Wernsdörfer [3]) found the skin in erythema annulare centrifugum hypersensitive to pilocarpine and epinephrine (Adrenalin), and Proppe [4] mentions the three cases of Erigushi and Imakito, and the two of Egiri, all with vagotonia.

Increased sensitivity to intradermal injections of trichophytin, epidermophytin, microsporin, Streptococcus filtrate, tuberculin, and peptone has been elicited by various investigators.

In considering such suggestive evidence it seems reasonable to conjecture that erythema annulare centrifugum, though a disease whose distinctive features preclude merging it with urticaria or dermatitis herpetiformis, is related to them. The fact that in most cases there is no perceptible connection with internal disease must not be overlooked.

In my case, the shock factor can be assumed to have been present, for the exploratory operation was followed by no mitigation of the distressful ascites. The autonomic nervous system may be able to produce erythema annulare centrifugum when stimulated by intestinal toxins, as Darier thought, bacterial toxins, shock, or worry, conscious or subconscious.

104 S. Michigan Ave. (3).

CUTANEOUS PAPILLOMATOSIS

Confluent and Reticulated Variety

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CONFLUENT and reticulated papillomatosis was first described in 1929 by Gougerot and Carteaud,[1] who observed the disorder to be characterized by papuloverrucous lesions which have a tendency to become confluent and which produce a reticulated pattern. These authors again discussed the condition in 1932 [2] and presented additional cases. Wise and Sachs,[3] in the first account of this dermatosis in the American literature, reviewed the clinical and microscopic features of a case in which the patient had been presented before the section on dermatology of the New York Academy of Medicine.[4]

A second American case of this disorder was recently observed and is herewith reported.

REPORT OF A CASE

M. W., a 32-year-old Negro Jamaican housewife, first entered the Dermatology Clinic of the New York Hospital in December, 1951. She presented an eruption of widespread distribution, which was asymptomatic. The dermatosis began in 1948 and first involved the anterior portion of the chest, the back, and the shoulders. According to the patient, improvement occurred after she had been given six x-ray treatments in fractional doses, but a relapse occurred three months later. A year before coming under our observation, the patient sought advice at another institution, where a biopsy was performed and diagnoses of parapsoriasis and lichen planus were suggested.

There was no contributory information in the family history. In the past history it was noted that four years ago she had been given quinine over a two-week period for the treatment of malaria. The menstrual history revealed amenorrhea for the months of February, September, October, and November, 1951. A normal menstrual period occurred in December, 1951, but it was followed by menorrhagia of a minor degree, lasting through January, 1952. Since February, 1952, the menses have been normal.

From the Department of Medicine (Dermatology), The New York Hospital and Cornell University Medical College.

1. Gougerot, H., and Carteaud, A.: Papillomatose papuleuse confluente et réticulée, Arch. dermat-syph. Hôp. St. Louis, Paris **1**:102 (March) 1929.

2. Gougerot, H., and Carteaud, A.: Neue Formen der Papillomatose, Arch. Dermat. u. Syph. **165**:232 (April) 1932.

3. Wise, F., and Sachs, W.: Cutaneous Papillomatoses: Papillomatose Confluente et Réticulée, Arch. Dermat. & Syph. **36**:475 (Sept.) 1937.

4. Wise, F.: Confluent and Reticular Papillomatosis (Gougerot and Carteaud), Arch. Dermat. & Syph. **35**:550 (March) 1937.

Examination revealed lesions over the upper chest, the breasts, and in the intermammary and epigastric regions. The axillae and scapular areas reaching to the lower dorsal region were also involved, and some lesions were noted on the thighs and arms. The scalp, palms, and soles were unaffected, as were the mucosal surfaces. The eruption comprised variously sized darkly pigmented papulosquamous oval lesions, whose largest diameter appeared to parallel the lines of cleavage. A finely lamellated hyperkeratotic scale could be removed by scratching. In most of the regions the individual lesions were well defined; however, in the sternal and spinal-scapular areas the separate lesions were less distinct, and the eruption assumed a confluent and reticulated configuration (Fig. 1).

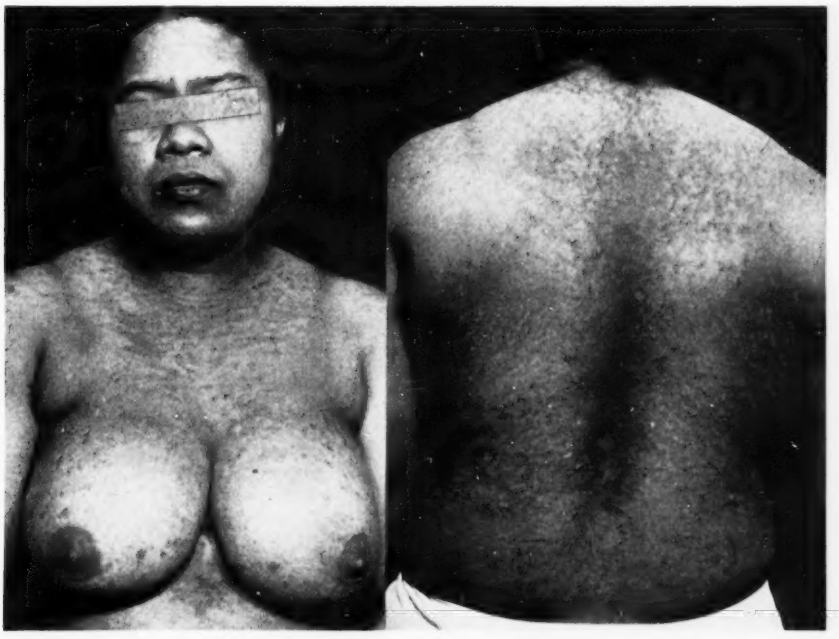

Fig. 1.—The lesions are distributed over the sternal and mammary areas and form a confluent and reticulated pattern over the back.

Routine blood studies and urinalysis gave normal results. The basal metabolic rate was −10; the cholesterol content was 278 mg. per 100 cc.; the cholesterol ester content was 200 mg. per 100 cc. (72%), and the serologic reaction for syphilis was negative.

Biopsy revealed the epidermis to be regularly acanthotic, verrucous, and covered by a moderately increased densely laminated horny layer. The rete pegs were broadened, and some were anastomosed. The granular layer was somewhat thinned, and the palisade layer revealed increased pigment but was otherwise unchanged. The vessels of the upper cutis, as well as the papillary capillaries, were dilated, and the endothelial cells appeared somewhat vesicular. There was moderate interstitial edema in the upper cutis and little or no cellular infiltration (Fig. 2.).

Treatment at first consisted of mild local medication, without response. Subsequently, a daily dose of ½ grain (0.03 gm.) of thyroid extract was prescribed on the basis of a mild hypothyroidism. After five weeks, the eruption was slightly improved. Further observation was impossible, as the patient failed to return and could not be found.

COMMENT

The distribution and clinical appearance of the eruption in the patient herewith reported closely simulated the original descriptions. Differential diagnosis includes seborrheic dermatitis, Darier's disease, epidermodysplasia verruciformis, verruca plana juvenilis, and acanthosis nigricans. Seborrheic dermatitis may be distinguished by its origin in the scalp, by the oily secretion and yellowish crust, and by its marked

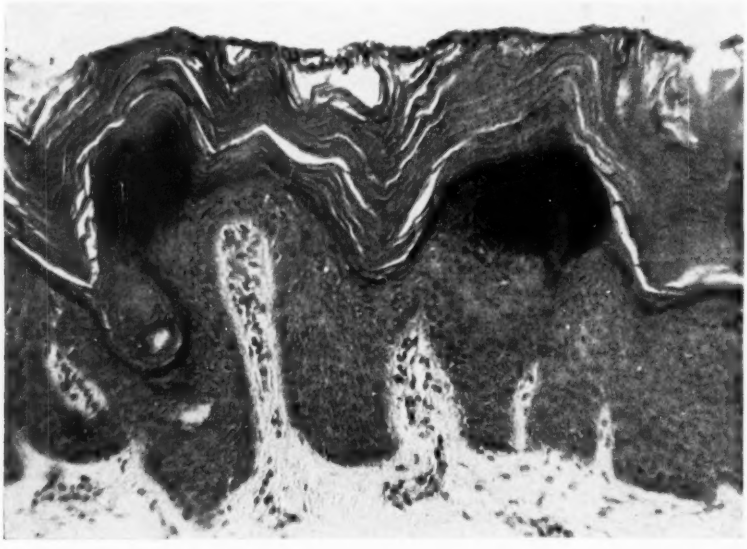

Fig. 2.—The epidermis is regularly acanthotic and verrucous. It is covered by a densely laminated horny layer. The basal layer is intact, and the reaction in the cutis is acellular.

inflammatory character. The primary lesion in Darier's disease is a crusted papule which may remain discrete or which, by coalescence, may produce irregularly shaped greasy plaques, sometimes vegetating, in which pigmentation is not a prominent feature. The sites of election are less localized than those of cutaneous papillomatosis, as Darier's disease may begin on the face and head and may spread to involve the extremities, the front of the chest, and the inguinal and gluteal regions. Epidermodysplasia verruciformis occurs early in life, and a history of parental consanguinity may be noted. The warty growths chiefly affect the extremities, particularly the dorsa of the hands; sometimes the face is involved. The small discrete dry warty lesions and the distribution of verruca plana juvenilis differentiate this entity. Acanthosis nigricans may closely simulate cutaneous papillomatosis; however, the occasional occurrence of the lesions in the mouth, the dark pigmentation, and the presence of malignancy are differentiating points.

The microscopic picture in this patient coincides with observations of others: 1. The epidermis is regularly acanthotic and verrucous. 2. It is covered by a densely laminated thickened horny layer. 3. The palisade layer is intact throughout. 4. The reaction in the cutis is acellular. These features clearly distinguish cutaneous papillomatosis from most of the other processes; however, acanthosis nigricans may be difficult to differentiate microscopically. The process is similar in both eruptions. The characteristic hyperkeratosis, the acanthosis with adjacent thinning of the epidermis, the melanin pigmentation, and the cellular infiltration in acanthosis nigricans are more pronounced than in cutaneous papillomatosis.

Although the cause of cutaneous papillomatosis is unknown, a precipitating factor may be an endocrine imbalance, possibly thyroid deficiency, as suggested by Gougerot and Carteaud,[2] and Wise and Sachs.[3] Slight improvement after thyroid medication in the case presented is of interest in this connection.

SUMMARY

The second American case of confluent and reticulated papillomatosis of Gougerot and Carteaud is presented.

Endocrine disturbance is mentioned as a possible precipitating factor, as earlier reports suggest.

PREMALIGNANT FIBROEPITHELIAL TUMORS OF SKIN

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MONROE, MICH.

THIS PRESENTATION is based on four cases of peculiar fibroepithelial tumors which were encountered among more than 900 epitheliomas examined during the three years from November, 1947, to November, 1950. It is believed that these tumors do not constitute a truly new entity, but, rather, that they are an unusual variety of basal-cell epithelioma. Similar cases doubtless have been seen by others and either did not attract particular interest or were interpreted in a different way. A fairly thorough search of the literature revealed two similar cases [1] and one with similar histologic features.[2] Other reports may have been missed, but no clearcut reference to this type of tumor was found in current textbooks or in recent discussions of epitheliomas.

The following cases were believed worthy of study because they presented diagnostic difficulties clinically as well as under the microscope, because the tumors exhibited unusual relations between parenchymatous and stromal elements, and because they seem to bring into focus some fundamental questions of the pathogenesis of epitheliomas.

The diagnostic difficulties are exemplified by the first case.

REPORT OF CASES

CASE 1.—The patient, a 67-year-old white woman, had acquired half a dozen tumors on the lower part of the back over a period of about five years. The lesions were raised plaques, flesh colored, sessile or slightly constricted at the base, and fairly soft in consistency. They measured 1 to 3 cm. in diameter. The largest lesion had an ulcerated and crusted center, otherwise there was no appreciable hyperkeratosis. Single sections of biopsies taken elsewhere showed the ulcerated tumor to be basal cell epithelioma, while one of the smaller lesions was interpreted as verruca senilis of the reticulated type. As this diagnosis did not fit the clinical

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From the Detroit Institute of Cancer Research and the Department of Dermatology, Wayne University College of Medicine, Detroit.

Read before the Section on Dermatology and Syphilology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 12, 1952.

1. (*a*) Waelsch, L.: Über die Verruca senilis und die aus ihr entstehenden Epitheliome, Arch. Dermat. u. Syph. **76**:31, 1905. (*b*) Sibley, K.: Seborrhœic Verrucae and Multiple Basal-Celled Epitheliomata, Proc. Roy. Soc. Med. **25**:670, 1932. Muende, I. K.: Seborrhœic Verrucae and Multiple Basal-Celled Epitheliomata, and Further Histological Report and Comment, ibid. **25**:927, 1932.

2. Danlos, Flandin, M. J., and Darier, J.: Epithéliomatose baso-cellulaire adénoide généralisée de la peau avec transformation maligne par endroits, Bull. Soc. franç. dermat. et Syph. **20**:379, 1909.

picture two other lesions were excised, and more or less serial sections were examined. These specimens and a pendunculated soft tumor which was removed from the groin two years later presented a remarkable histologic picture, which is illustrated in Figure 1*A*. The structure is strikingly similar to an intracanalicular fibroadenoma of the mamma (Fig. 1*B*), except that the epithelium of the cutaneous tumors is not glandular in type and has many connections with the epidermis which covers it. Closer examination showed that this is basal-cell epithelioma in

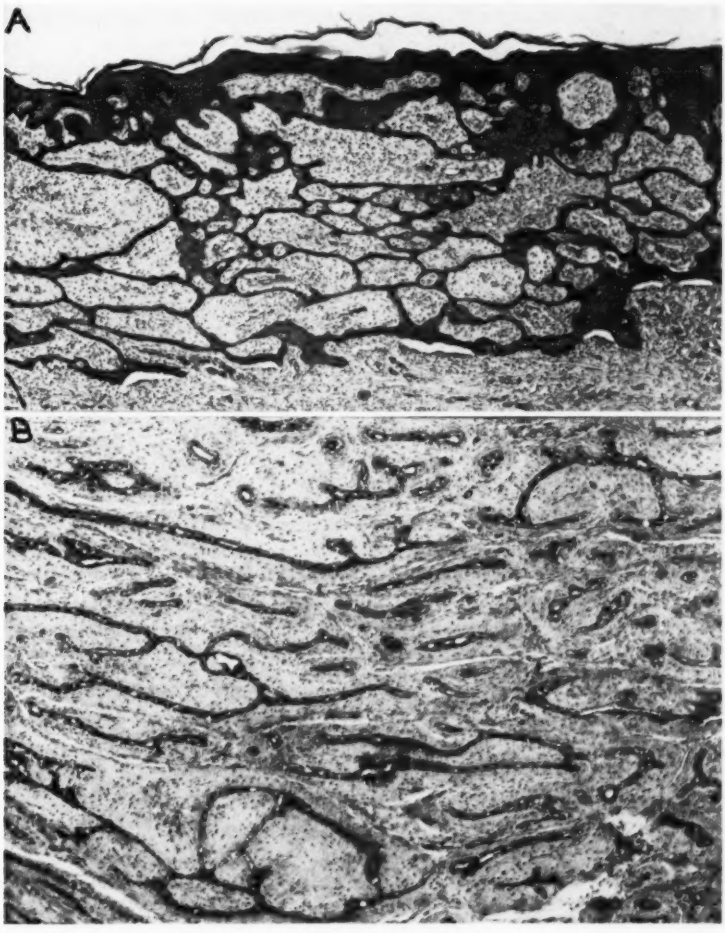

Fig. 1.—Comparison of premalignant fibroepithelial tumor of skin and intracanalicular fibroadenoma of mamma. *A* (Case 1), tumor from groin. *B*, fibroadenoma of breast. The section from which this photomicrograph was taken was supplied by Henry Tesluk, M. D., Director, Michigan Tumor Registry, Detroit. Both sections stained with hematoxylin and eosin and reproduced at identical magnification.

which the epithelium is overwhelmed by the excessive formation of fibrous tissue. The stroma grows into the epitheliomatous nests and compresses them into thin anastomosing septa which on cross section may be mistaken for tubular structures or for the strands of a net.

It is interesting to note that the patient also had a typical rodent ulcer above the left eyebrow which on histologic examination was found to be a basal-cell epithelioma of the common type, without excessive formation of stroma. The patient's past history included removal of a kidney for a tumor which was reported to be adenocarcinoma.

CASE 2.—A few months after the first patient had been examined, a biopsy was submitted on "a flat coin-shaped lesion with active edge and slightly eroded center." No other data were available except that the tumor was located on the trunk of a woman patient. The histologic picture (Fig. 2*A*) showed epithelial masses beneath the epidermis with which they were in multiple contact, but from which they were sharply demarcated because they consisted of basal-type cells.

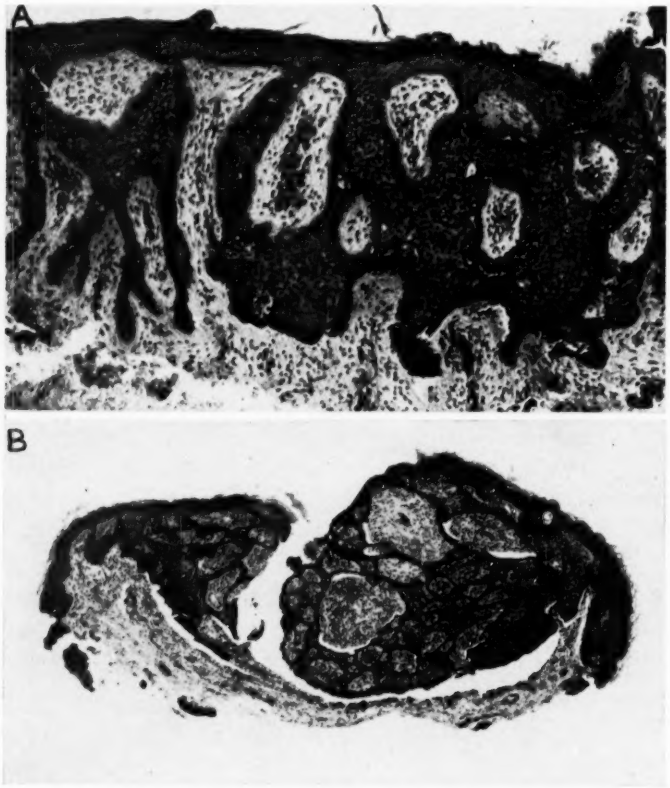

Fig. 2.—*A* (Case 2), superficial basal cell epithelioma with hyperplasia of the connective tissue stroma. Note the resemblance to the reticulated type of verruca senilis. *B* (Case 3), small pedunculated tumor from groin. Both sections stained with hematoxylin and eosin.

Depending on the point of view of the observer, one could say that solid masses of epithelioma were encroached upon and compressed by fibrous tissue, or that branching and anastomosing ridges and septa of epithelium divided the vascular connective tissue into compartments. It is very likely that the simultaneous and interdependent growth of epithelium and connective tissue resulted in the complicated structure.

CASE 3.—The third case was that of a white man, 55 years of age, who presented three small tumors, one in the right groin and two in the left. The tumors were pink or reddish, soft to the touch, ranging from 2 to 5 mm. in diameter. One was a flat nodule with a broad base, and the other two were pedunculated. The clinical impression was that of papillomas. The patient had

had one testicle removed for malignant seminoma several years before, and that was the main reason for his concern over the skin lesions which he said had not been present more than two months. Histologic examination (Fig. 2*B*) showed a picture very similar to the other cases. A fibromatous stroma was traversed by strands and septa of compressed epithelium resembling basal-cell epithelioma.

CASE 4.—The last case was the most instructive one in several respects. The patient was a 51-year-old man of Dutch extraction who had had what he called warts on his back for several years. Some of these he said had become sore and larger when he took heat and massage treatments for the relief of lower back pain. On examination, the upper part of the patient's back presented many small and large senile warts (seborrheic keratoses) of typical appearance, with greasy yellow and brown scales. On the lower part, near the waistline, there was a roughly oval

Fig. 3 (Case 4).—Back of the patient after six lesions had been removed. The sites of removed tumors, and of those still present are indicated by numbers. For details see text. Many senile verrucae are present on the upper part of the back.

plaque (lesion 1), 5 by 2.5 cm. in diameter, flat, but with a fungating bleeding mass in the center, situated left to the spine. Two pink macular lesions, measuring 6 by 3 mm., with atrophic center and thread-like border, quite typical of the superficial type of basal-cell epithelioma, were present on the right side, one near the waist (lesion 5), the other over the posterior iliac spine (lesion 8). In addition, there were seven peculiar fleshy pink papules or plaques, with a smooth or slightly nodular surface, and either plateau-like and broad-based or somewhat pedunculated. They were situated on both sides of the back near and above the waistline. While some resembled either seborrheic warts or epitheliomas, most of them rather looked and felt like fibromas. Unfortunately, the patient was not photographed at his first visit, but Figure 3 shows his back when six of the lesions had already been removed. Figure 4*A* is a close-up view of the largest

remaining tumor (lesion *9*), which forms a somewhat nodular plaque with constricted base. Nearby is one of the smaller lesions (lesion *10*) and some senile warts.

In three sittings, all the 10 lesions mentioned and a large typical verruca senilis (lesion *11*) were removed either by excision and suture, or by curettage followed by fulguration. Microscopic examination of the greasy-scaled wart from the upper back showed a papilloma with horny recesses and cysts in the epidermoid epithelium, in short, the typical picture of seborrheic keratosis (verruca senilis). The histologic character of the other lesions varied from typical superficial basal cell epithelioma in the macular lesions *5* and *8* to basal cell epithelioma with excessive stroma formation in lesions *1*, *2*, and *6*, and to the "intracanalicular" type of structure (lesions *3*, *4*, *7*, *9*, *10*) which had been present in the other cases (Fig. 4*B* and 6*A*). Several specimens offered highly instructive pictures, which permit the formation of an opinion concerning the morphogenesis of these tumors.

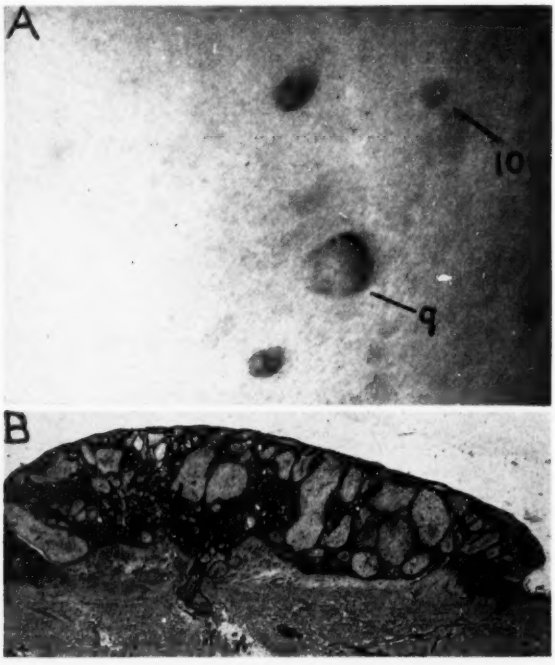

Fig. 4 (Case 4).—*A*, close-up view of lesions 9 and 10. Several verrucae seniles present nearby. *B*, low-power view of a section of lesion 9, showing the resemblance to the intracanalicular fibroadenoma of the mamma and also to the reticulated type of verruca senilis. Section stained with hematoxylin and eosin.

A rather flat plaque (lesion *7*) has a structure which resembles that of the reticulated type of verruca senilis (Fig. 5*A*). However, there is a complete absence of the horny recesses and cysts which usually are found in the verruca. Our lesion does not show any hyperkeratosis, and a thin continuous epidermis covers the surface. The epithelial structures are embedded in a solid layer of newly formed vascular fibrous tissue which extends for some distance below the deepest epithelial penetration and replaces the papillary and subpapillary strata of the corium. The pars reticularis cutis is unaffected below the entire new growth. Serial sections prove that even the thin, two-celled rows of epithelium are cross sections of thin septa rather than strands of a net. The peripheral parts of the plaque show simpler structure (Fig. 5*B*). Here, the impression is gained that rete ridges are stretched long and are molded by hypertrophic vascular

fibrous tissue, which differs from the normal papillary and subpapillary connective tissue. Beyond the periphery of the actual plaque, there are spots which can be recognized only in comparison with the more developed stages. Here (Fig. 5 C) there is hardly any noticeable change of the epidermis, but there is increased vascularity of the subepithelial connective tissue, with an increased number of connective tissue cells. These findings seem to indicate that in this particular lesion mesodermal changes are present as early or perhaps even earlier than visible

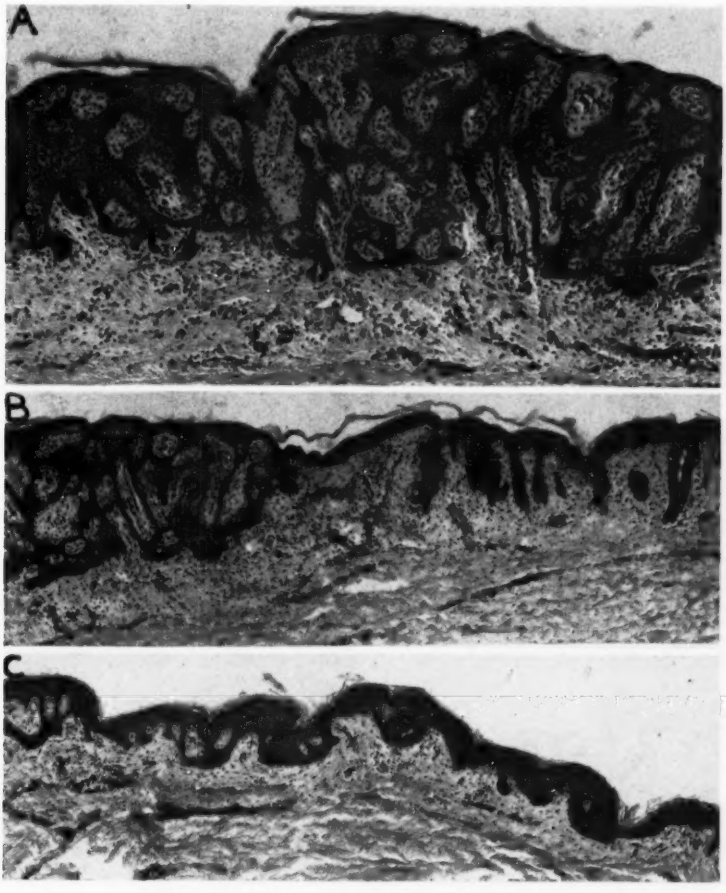

Fig. 5 (Case 4, lesion 7).—Sections stained with hematoxylin and eosin. *A*, details of central part of tumor. *B*, edge of tumor. *C*, area beyond edge of clinical lesion. For description see text.

epithelial alterations. There is some resemblance to Biberstein's[3] cases of fibromas with atypical epithelial proliferation, but no actual fibroma or histiocytoma is present in the deeper parts of the corium.

Lesion *4*, a broadly pedunculated elevated plaque of irregular outline, measuring about 1.5 by 1.5 cm., reveals once again the striking similarity with the intracanalicular fibroadenoma of

3. Biberstein, H.: Fibrome mit atypischer Epithelwucherung, Arch. Dermat. u. Syph. **164**:69, 1931.

the mamma. This is due to the massive hypertrophy of the fibrous element. The various parts of the stroma have different structures. Some compartments consist of dense mature fibrous tissue,, others are more finely fibrillar, and still others have the loose, almost myxomatous appearance which sometimes is found between normal sweat coils and also in basal-cell epitheliomas. The epithelial part of the tumor is composed of relatively small but fairly light-staining cells resembling those of the epidermis. The most peculiar feature of this lesion is that there are numerous small clumps of dark-staining cells in palisade arrangement which are sitting at one or both sides of the thin epithelial septa, like buds on a branch. The distinction between these "basal cell" buds and the lighter-staining cells of the septa is always sharp (Fig. 6*B*). These buds can be interpreted either as tiny basal cell epitheliomas or as rudimentary hair germs.

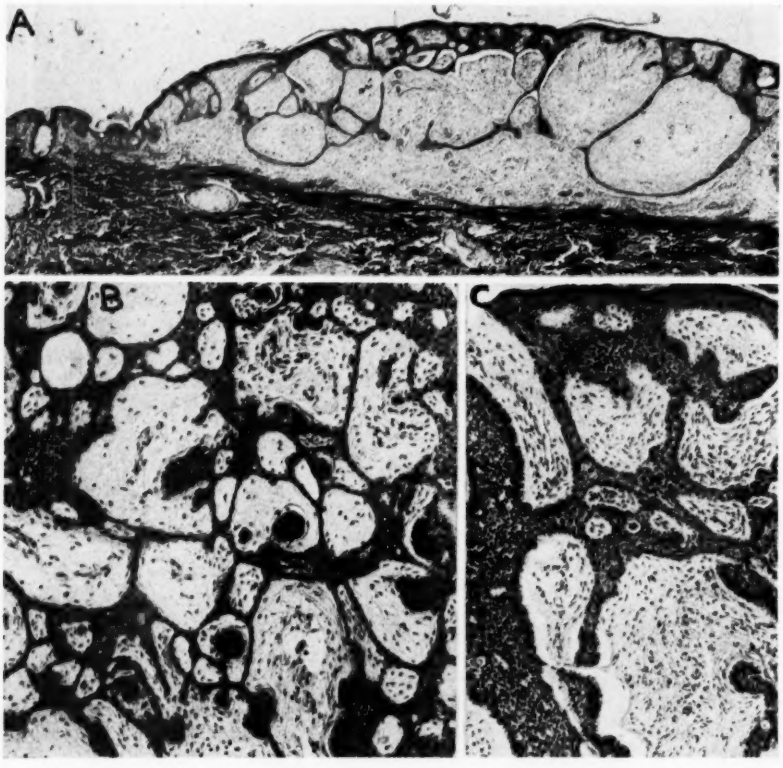

Fig. 6 (Case 4).—*A*, lesion 10, section stained with acid orcein and Giemsa solutions. The bulk of the tumor consists of newly formed fibrous tissue which stains light because it contains no elastic fibers. The stroma compresses the epithelium into thin septa and keeps it out of the corium proper. *B*, detail of tumor 4, section stained with hematoxylin and eosin. Multiple buds of basal type epithelium arising from, and in some cases surround, the septa of lighter-staining epithelium. *C*, detail of lesion 3, sections stained with hematoxylin and eosin. The left part of the picture shows basal cell epithelioma while the right half shows septa of epidermoid epithelium from which spring smaller buds of basal type cells (*B*).

In a few places, they have grown into somewhat larger masses, and then they usually have completely replaced the mother tissue of lighter-staining cells. In these places there can be no doubt that one is dealing with basal-cell epitheliomas. These sections strongly suggest the multicentric origin of basal-cell epitheliomas from the more highly differentiated epithelial part of the benign fibroepithelioma.

Lesion 3, a similar but somewhat smaller pink fleshy plaque, shows full-blown basal-cell epithelioma which has replaced the septa of lighter-staining cells to a large extent (Fig. 6*C*). However, at several points, small basal-cell buds are discernible, and by examination of serial section two isolated clumps of cells were found, one of which extends through five sections of 10 μ thickness, the other through six. Neither of these buds has any connection with any other area of basal-cell structure but they are attached to one of the more differentiated epithelial septa

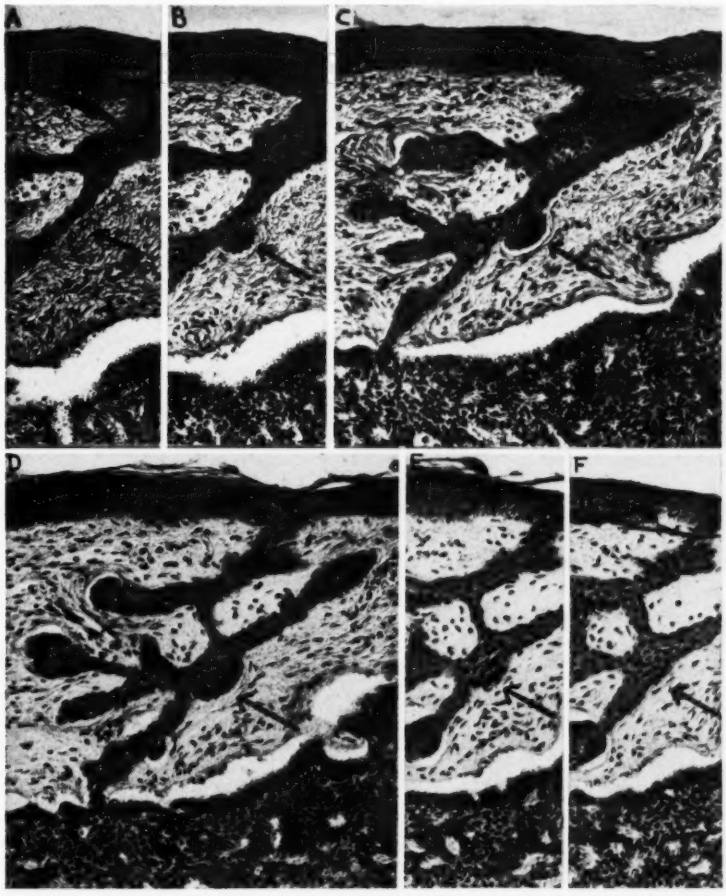

Fig. 7 (Case 4).—A series of 10 μ sections from lesion 3. *A* to *C* stained with hematoxylin and picric acid-ponceau (modified Van Gieson solution), *D* to *F* stained with hematoxylin and eosin. In the lower part of the pictures, a mass of basal cell epithelioma is visible. Between it and the epidermis stretch septa of epidermoid epithelium. From these septa arise several tiny basal cell epitheliomas. The one indicated by the arrow is completely contained in the four sections *B*, *C*, *D*, *E* and has no connection with the larger mass of epithelioma.

(Fig. 7). These two spots seem to prove beyond any reasonable doubt not only that the basal-cell epithelioma in this lesion has a multicentric origin, but also that basal-cell epithelioma can arise ***de novo*** in the epithelium of a benign tumor of the skin, without any close relationship to preformed adnexal structures, either adult or embryonic.

COMMENT

Of the four cases presented, three (Cases 1, 3, and 4) showed skin tumors with very similar histologic characteristics, while Case 2 seems to form a link to those relatively common cases of superficial epitheliomatosis which exhibit considerable development of fibrous stroma. The clinical picture of the same three cases (1, 3, and 4) also showed marked and peculiar similarities. All three patients had multiple tumors situated either in the lumbar region or in the groin. These tumors gave the clinical impression of papillomas or sessile fibromas because they looked and felt "fleshy," formed broad-based flat plaques or pedunculated elevations, and had a smooth or nodular surface without appreciable hyperkeratosis. Their color was pink or reddish, in some instances with a tinge of brown. In two cases, one or several of the lesions went on to form fungating ulcerated tumors. Two of the patients had been operated on for malignant tumors of the genitourinary tract, but these tumors had apparently been eradicated, and there was no sign of recurrence or metastasis at the time the skin lesions were observed. No evidence of internal malignancy was found in the third patient.

This man (Case 4) presented typical verrucae seniles, typical basal cell epitheliomas, and the fibroepithelial tumors side by side. There was highly suggestive evidence that some of the basal cell epitheliomas arose in multiple centers in the fibroepitheliomas. Because considerable similarity to the reticulated type of verruca senilis is evident in several of the tumors while others are obvious basal-cell epitheliomas with excessive formation of stroma, the question of whether we are dealing here with transformation of verrucae seniles into basal cell epitheliomas must be considered.

I do not believe that this is the case, and Figure 8 shows the differences in diagrammatic fashion. Figure 8*A* is a diagram of normal skin with the pilosebaceous follicle. The various parts are identified by differential shading. The lower left diagram (Fig. 8*C*) shows the papillomatous changes which characterize verruca senilis. The epithelium resembles the epidermis; the stroma resembles the papillary layer. This is a benign epidermal neoplasm in Becker's[4] sense, growing upward out of the skin. The right upper diagram (Fig. 8*B*) shows the usual type of superficial basal-cell epithelioma. It grows along the lower border of the epidermis and downward into the corium, part of which it replaces. Its epithelium resembles adnexal epithelium, and it is enveloped in connective tissue corresponding to the fibrous outer-root sheath or the stromal envelope of the coil glands. Finally, the lower right corner (Fig. 8*D*) shows fibroepitheliomas. The epithelium, which may be either of epidermoid or of adnexal type, grows downward from the epidermis, but it is continuously pushed upward and compressed into thin septa by the excessive development of buds of "adnexal type" stroma which keep the entire tumor out of the corium proper and thus render it a noninvasive "premalignant" type of lesion.

This interpretation is supported by the facts that the horny recesses and cysts which characterize all types of verruca senilis are not found in these tumors, and that the stroma is not the loose papillary type, but dense fibrous or edematous or myxomatous tissue, as it is also found in the intracanalicular fibroadenomas of the mamma and in basal-cell epitheliomas. These cases, therefore, do not add evidence

4. Becker, S. W.: Benign Epidermal Neoplasms, Arch. Dermat & Syph. **26**:838, 1932.

for the thesis that verrucae seniles may give rise to basal cell epitheliomas, but rather urge a reinterpretation of those published cases in which that development was assumed. Unfortunately, few of these cases were published with data sufficient for reinterpretation. One of the exceptions is Waelsch's case,[1m] and his pictures suggest that he may have been dealing with a lesion similar to the tumors described here. My own case,[5] in which basal cell epithelioma was encountered on the face of the patient underneath one of many senile warts present, and which is occasionally quoted in support of the thesis of transformation, I am now inclined to consider as being a mere coincidence of occurrence of two relatively common skin tumors.

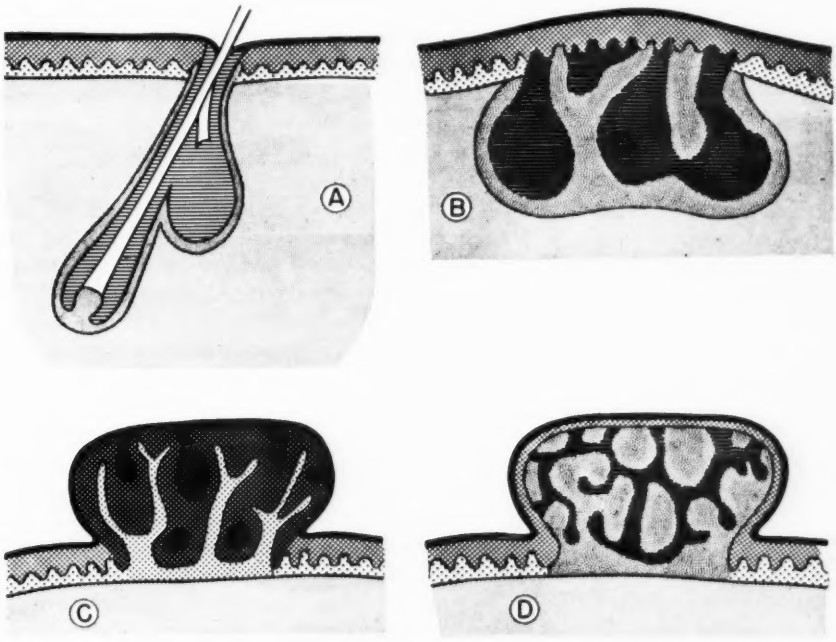

Fig. 8.—Diagrams illustrating the histogenesis of the tumors under discussion. *A*, normal skin, *B*, superficial basal cell epithelioma; *C*, verruca senilis; *D*, premalignant fibroepithelial tumor. The following symbols have been used: epidermis and epidermoid epithelium—cross-hatched; adnexal epithelium and tumor epithelium resembling it—horizontal lines; papillary connective tissue and stroma resembling it—regularly spaced dots; adnexal connective tissue sheath and stroma resembling it—stipples; pars reticularis cutis—gray; keratin—black.

GENERAL CONSIDERATIONS

The remaining space will be used for a presentation of some thoughts engendered by the study of these cases and which concern the histogenesis and diagnosis of epitheliomas in general. No claim is made that any completely new ideas are proposed. So much has been said and written about skin cancer in the last 50 years that almost every possibility has been discussed, and it is often difficult

5. Pinkus, H.: Über einen Fall von Basalzellenepitheliom auf Verruca senilis, Arch. Dermat. u. Syph. **169**:58, 1933.

to trace ideas to their original source. It is my intention to present my own conclusions and to emphasize a few points which have not been given much attention in recent discussions.

Ever since Krompecher [6] established that skin tumors composed of small dark-staining cells are epithelial tumors for which he claimed derivation from the basal layer, there has been a logical difficulty which has been mentioned, among others, by Dubreuilh and Auché,[7] Darier,[8] Foot,[9] and Eichenlaub and Osbourn.[10] The last authors wrote: "Inquiry into the pathogenesis of epitheliomata reveals an apparent paradox in the activities of the epidermal cells. If we consider the basal cells as the parent cells of the prickle cells, then we have the more primitive cell giving rise to the less malignant tumor." In other words, if the basal cell is the undifferentiated matrix cell of the prickle cells, one should expect epidermoid carcinoma as it gets less differentiated to approach more and more the basal-cell type. Grade IV (Broders) prickle-cell carcinoma should be synonymous with basal-cell epithelioma. We all know that this is not so. While the cells of the two kinds of tumor may resemble each other in the stained section, there are vast differences in their clinical behavior and prognosis.

Various authors have tried to explain the difference by showing that the two types of carcinoma are not derived from the same type of cell. According to Dubreuilh and Auché [11] the Fox brothers were the first to propose derivation of the rodent ulcer cells from hair follicles, while Verneuil favored sweat gland origin. Dubreuilh and Auché (1901) stated that on the basis of 23 cases in which examination was made in serial sections the small-celled epitheliomas usually arise from the pilosebaceous follicles, most frequently from the neck of the follicle, less frequently from the level of the sebaceous gland or from the junction of follicle and epidermis. Borrmann (1904),[12] who examined serial sections of 265 small skin cancers, 80 of which were of the basal-cell variety, thought he could trace all the latter to aberrant epithelial germs, which he theorized were separated from the epidermis during the closure of the facial clefts or during the genesis of the adnexa. He expressed this view in the unfortunate term "corium carcinoma," which may be one reason why his painstaking and diligently documented work has been completely overlooked in recent articles. Mallory (1910)[13] coined the name "hair matrix tumors," which expressed his views. The adnexal origin continued to be favored in England, for

6. Krompecher, E.: Der drüsenartige Oberflächen-Epithelkrebs: (Carcinoma epitheliale adenoides), Beitr. path. Anat. **28**:1, 1900; Der Basalzellenkrebs, Jena, Gustav Fischer Verlag, 1903.

7. Dubreuilh, W., and Auché, B.: Diagnostic clinique et histologique de l'ulcus rodens, Ann. dermat. et syph. **3**:318, 1902.

8. Darier, J.: Des épithéliomes primitifs de la peau, Brit. J. Dermat. **34**:145, 1922.

9. Foot, N. C.: Adnexal Carcinoma of the Skin, Am. J. Path. **23**:1, 1947.

10. Eichenlaub, F. J., and Osbourn, R. A.: Studies in the Histogenesis of the Epidermis, A. M. A. Arch. Dermat. & Syph. **64**:700, 1951.

11. Dubreuilh, W., and Auché, B.: De l'ulcus rodens: Clinique et anatomie pathologique, Ann. dermat. et syph. **2**:705, 1901.

12. Borrmann, R.: Die Entstehung und das Wachstum des Hautcarcinoms nebst Bemerkungen über die Entstehung der Geschwülste im Allgemeinen, Ztschr. Krebsforsch. **2**:1, 1904.

13. Mallory, F. B.: Recent Progress in the Microscopic Anatomy and Differentiation of Cancer, J. A. M. A. **55**:1513, 1910.

instance, by Adamson,[14] and in France, for instance, by Favre, Josserand, and Martin.[15] In this country, Foot [9] recently came to conclusions ("adnexal carcinoma") quite similar to those of Dubreuilh and Auché,[11] while Lever's [16] conclusions resemble those of Borrmann [12] insofar as he derives basal-cell epithelioma from the primary epithelial germ which in embryonic life forms hair follicles, sebaceous and apocrine glands. Lever agrees with Adamson [14] in the important consideration of basal-cell tumors not as carcinomas but as hamartomas and as being related to other benign nevoid tumors of the appendages.

All these authors and many others not mentioned have this in common—they consider basal-cell epithelioma to be derived from adnexal epithelium, either in its adult or embryonic form, while prickle-cell carcinoma derives from the epidermis proper.

Eichenlaub and Osbourn,[10] on the other hand, have tried to show by examination of the skin of the pig embryo that the primitive stratum germinativum gives rise to two independent types of cell in the epidermis—the basal cells and the squamous cells, and that either layer propagates itself independently. Van Scott [17] favors a similar view on the basis of the different enzymatic constitution of these layers. Thüringer [18] had suggested the independence of basal layer and higher strata in adult life on the basis of mitotic counts, which showed relatively more mitoses in the higher strata. Eichenlaub and Osbourn suggest that the prickle cells are the primary functional cells of the epidermis proper, and that this may explain the greater malignancy of the epitheliomas derived from them.

The two types of explanation mentioned in the preceding paragraphs have in common that they presuppose the independent and not interchangeable nature and propensities of the cells which form prickle-cell cancers and basal cell cancers. Consequently, it is argued, tumors derived from one source may have properties different from derivatives of the other. A survey of the literature on epidermal regeneration and my own studies on tissue cultures [19] and on stimulated epidermis [20] have raised doubts in my mind about the applicability of these explanations.

14. Adamson, H. G.: On the Nature of Rodent Ulcer: Its Relationship to Epithelioma Adenoides Cysticum of Brooke and to Other Tricho-Epitheliomata of Benign, Nevoid Character; Its Distinction from Malignant Carcinoma, Lancet **1**:810, 1914.

15. Favre, M.; Josserand, A., and Martin, J. F.: Tumeurs malignes cutanées épithéliales, in Darier, J. and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, Vol. 6, p. 693.

16. Lever, W. F.: Pathogenesis of Benign Tumors of the Cutaneous Appendages and of Basal Cell Epithelioma: I. Benign Tumors of the Cutaneous Appendages, Arch. Dermat. & Syph. **57**:679, 1948; II. Basal Cell Epithelioma, ibid. **57**:709, 1948.

17. Van Scott, E. J.: Studies on the Arginase Activity of the Skin, J. Invest. Dermat. **17**:21, 1951; Arginase Activity in Human Skin, Science **113**:601, 1951.

18. Thüringer, J. M.: Studies on Cell Division in the Human Epidermis, Anat. Rec. **40**:1, 1928. Thüringer, J. M., and Cooper, Z. K.: The Mitotic Index of the Human Epidermis, the Site of Maximum Cell Proliferation, and the Development of the Epidermal Pattern, abstracted, Anat. Rec. **106**:255, 1950.

19. Pinkus, H.: Über Gewebekulturen menschlicher Epidermis: Ein Beitrag zur Anatomie der Haut, Arch. Dermat. u. Syph. **165**:53, 1932.

20. Pinkus, H.: Examination of the Epidermis by the Strip Method of Removing Horny Layers: I. Observations on Thickness of the Horny Layer, and on Mitotic Activity After Stripping, J. Invest. Dermat. **16**:383, 1951; II. Biometric Data on Regeneration of the Human Epidermis, J. Invest. Dermat. **19**:431, 1952.

Adult human epidermis can be stimulated to rapid proliferation by stripping away the horny layer. This can be done conveniently and gently by the repeated application of a pressure-sensitive adhesive tape (Scotch Tape). When all the horny layer has been removed, as much as 4% of the remaining cells can be found in mitosis 48 to 72 hours later. Under these conditions, about equal numbers of mitoses occur in the basal layer and in the one immediately above it. Few mitoses are seen in higher strata. There can be no doubt that at a time of rapid regeneration of the horny layer the basal cells furnish a large number of new prickle cells by mitotic division, while at the same time prickle cells add to the supply by dividing also. But even before active mitosis sets in, basal cells are directly converted into prickle cells. During the first 36 hours the individual basal cells increase greatly in size, so that smaller numbers are sufficient to cover the dermal junction. Others are squeezed out of the basal layer into the higher strata.

In tissue cultures, after the first few days (Pinkus [19]), and in human epidermis transplanted into irradiated rats (Toolan [21]) it is the basal layer which survives and forms new prickle cells and keratin.

On the other hand, if the entire epidermis has to be replaced, as in the healing of wounds, most authors agree (von Bardeleben,[22] Werner,[23] Loeb,[24] Hartwell,[25] Arey,[26] Firket [27]) that it is mainly the lower prickle-cell strata which became mobilized and flow over the denuded surfaces and epithelize them. When epithelization of the defect is complete, those cells which are in contact with the mesoderm form a new basal layer. Thus, not only does basal cell become prickle cell, but prickle cell can become basal cell. Moreover, in any larger denuded wound, for instance, in burns or in the donor sites of split-thickness skin grafts, the remnants of the adnexal epithelium grow upward and take active part in the epithelization of the surface. Here, adnexal epithelium forms epidermis.

It is necessary only to mention that in embryonic life the epidermis forms the adnexa. That this can happen in postnatal life has been denied dogmatically, and the —admittedly few—experimental and clinical data which suggest that adnexa can be newly formed in adult life have attracted little attention. Many years ago Ribbert [28] showed that repeated removal of epidermis on the rabbit's ear leads to new formation of sebaceous glands and even of hairs from the regenerated hypertrophic epidermis,

21. Toolan, H. W.: Proliferation and Vascularization of Adult Human Epithelium in Subcutaneous Tissues of X-Irradiated Heterologous Hosts, Proc. Soc. Exper. Biol. & Med. **78**:540, 1951.

22. von Bardeleben, H.: Die Heilung der Epidermis, Arch. path. Anat. **163**:497, 1901.

23. Werner, R.: Experimentelle Epithelstudien: Über Wachstum, Regeneration, Amitosen- und Riesenzellenbildung des Epithels, Beitr. klin. Chir. **34**:1, 1902.

24. Loeb, L.: A Comparative Study of the Mechanism of Wound Healing, J. M. Res. **41**:247, 1920.

25. Hartwell, S. W.: Surgical Wounds in Human Beings: A Histologic Study of Healing with Practical Applications; I. Epithelial Healing, Arch. Surg. **19**:835, 1929.

26. Arey, L. B.: Wound Healing, Physiol. Rev. **16**:327, 1936.

27. Firket, H.: Recherches sur la régénération de la peau de mammifère: I. Introduction et étude histologique, Arch. biol. **62**:309, 1951.

28. Ribbert, H.: Über die Neubildung von Talgdrüsen, Arch. Entwcklngsmechn. Organ. **18**:578, 1904.

and Gurewitsch [29] extended and confirmed these findings. More recently, it was shown by Silberberg and Silberberg [30] that the skin of guinea pigs when painted with methylcholanthrene produces new hairs by the budding of follicular and also of surface epithelium. Taylor [31] found that in rat skin which was devitalized by freezing new follicles and hairs will form after several months from the epidermis which has covered the defect. There is at least one clinical case on record (Planner [32]) in which human abdominal skin which had become hypertrophic around a jejunal fistula of long standing produced new sebaceous glands, coil glands of apocrine type, and even rudimentary hair papillae. Kyrle [33] thought that the new formation of sebaceous glands from the epidermis is a common occurrence in rhinophyma.

In short, it appears that basal cells, prickle cells, and adnexal epithelium are equally potent sources of epidermis, and, more rarely, also of adnexa, even in adult life. If that is true, then we can not explain the differences between prickle-cell tumors and basal-cell tumors by the different potentialities of their cells of origin.

The concept of embryonic rest origin for basal-cell epitheliomas remains to be discussed. Supposedly, an arrested embryonic germ is a group of cells which has been set apart during embryonic life and has not taken part in the later differentiation of the surrounding tissues. Formulated in another way, this means that these cells have emancipated themselves at the time of their "arrest" from the regulatory influences of the organism. Now it is one of the chief characteristics of embryonic cells that they do obey these regulatory influences and in due time become differentiated. On the other hand, it is one of the principal characteristics of tumor cells that they do not obey the normal regulations of the body. It seems to follow that an "arrested" embryonic cell becomes a tumor cell at the moment of its emancipation. In the foregoing comments I have tried to show that the various derivatives of the mammalian ectoderm retain quasi-embryonic potentialities into adult life. It is then much simpler to assume that adult but pluripotential cells become emancipated and are changed into tumor cells at the time the epithelioma actually begins to grow. The introduction of a tumor anlage which remains dormant for years and decades before it begins to proliferate becomes an unnecessarily complicated hypothesis.

Moreover, there is some evidence that carcinogenic agents such as certain petroleum products (Sunderland, Smith and Sugiura [34]), arsenic (Anderson,[35] Arhelger

29. Gurewitsch, B.: Über Neubildung von Talgdrüsen, Berlin, H. Blanke, 1910; reviewed in Jahresb. ü. Leistung. ges. Med. **45**:739, 1911.

30. Silberberg, M., and Silberberg, R.: Hair Growth in the Skin of Guinea Pigs Painted with 20-Methylcholanthrene, Arch. Path. **44**:297, 1947.

31. Taylor, A. C.: Survival of Rat Skin and Changes in Hair Pigmentation Following Freezing, J. Exper. Zool. **110**:77, 1949.

32. Planner, H.: Beitrag zur Frage der Neubildungsmöglichkeit der Hautdrüsen, Arch. Dermat. u. Syph. **146**:28, 1923.

33. Kyrle, J.: Vorlesungen über Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Springer-Verlag, 1925, Vol. 1.

34. Sunderland, D. A.; Smith, W. E., and Sugiura, K.: The Pathology and Growth Behavior of Experimental Tumors Induced by Certain Petroleum Products, Cancer **4**:1232, 1951.

35. Anderson, N. P.: Bowen's Precancerous Dermatosis and Multiple Benign Superficial Epithelioma: Evidence of Arsenic as an Etiologic Agent, Arch. Dermat. & Syph. **26**:1052, 1932.

and Kremen [36]), or x-rays (Anderson and Anderson [37]) can produce basal-cell epitheliomas in animal or human skin. It must also be kept in mind that the primary epithelial germ is a transient embryonic structure which almost immediately becomes differentiated into the adnexa derived from it. A primary epithelial germ, if it would persist into adult life, and particularly if we reduce it to its simplest imaginable form of one cell, is not different from, but is actually synonymous with, the pluripotential cell that has been shown to exist in the adult epithelial structures.

Summing up what has been said, it seems to follow that epidermoid carcinomas as well as basal cell epitheliomas have a common source, namely, the pluripotential adult epithelial cells. The explanation of the obvious differences between the two classes of tumors must be sought in other directions. Kyrle [38] expressed this thought when he said that the epidermis has two functions to fulfill and therefore possesses two different potentialities for differentiation. On the one hand, according to Kyrle, the germinal layer functions as surface epithelium and forms keratin; on the other hand, it is the matrix for postnatal new formation of sebaceous glands and proliferates as gland-like cords. Kyrle concluded that squamous-cell carcinomas or basal-cell epitheliomas result depending on whether the "one" or the "other" kind of epidermis furnishes the tumor growth. It may be even more to the point to say that the type of tumor depends on which one of the several potentialities of the pluripotential epithelial cells is activated.

This formulation is purely descriptive and does not attempt to explain cause or mechanism of tumor formation beyond the implication that the pluripotential cell undergoes a heritable change when it becomes a tumor cell and that its future course depends on the nature of this change. Basal-cell epithelioma results when the adnexal potentiality is activated, but differentiation is so low that only formless masses of cells are produced. Instead of contributing to the argument about histogenetic derivation which has been conducted indecisively for over 50 years and which by its very nature can not be solved by descriptive histology (Pullinger [39]), this concept simply states the undeniable fact that basal-cell epithelioma and so-called adnexal or organoid tumors of the skin "resemble" one or several of the normal appendages. Such a factual classification appears to be fully satisfactory for the practical purpose of diagnosis and prognosis. The accompanying Table, which is slightly modified from one published in 1938,[40] illustrates the point.

One of the most important points of this classification is the realization that resemblance of a tumor to epidermis or to cutaneous appendages must necessarily include the relationship between the epithelium and the subtending mesodermal sheath, which is a constant one in the normal state and is expressed in specific differentiations of both epithelium and connective tissue. It is reasonable to assume that these differentiations are, at least in part, due to the mutual influences of the two

36. Arhelger, S. W., and Kremen, A. J.: Arsenical Epitheliomas of Medicinal Origin, Surgery **30**:977, 1951.

37. Anderson, N. P., and Anderson, H. E.: Development of Basal Cell Epithelioma as a Consequence of Radiodermatitis, A. M. A. Arch. Dermat. & Syph. **63**:586, 1951.

38. Kyrle, J.: Beitrag zur Frage der Basalzellengeschwülste der Haut, Arch. Dermat. u. Syph. **121**:246, 1915.

39. Pullinger, B. D.: The Significance of Functional Differentiation in Mammary Tumors, Lancet **2**:823, 1949.

40. Pinkus, H.: Some Uncommon Skin Tumors, J. Michigan M. Soc. **37**:533, 1938.

components on each other. Study of the four tumors on which this paper is based and examination of a large number of prickle-cell carcinomas and basal-cell epitheliomas impressed me with the thought that perhaps there is an essential difference in the relationship between tumor epithelium and tumor stroma in the two groups. Prickle-cell cancer seems to have no other relationship to stroma than that of a cannibalistic foe to his enemy. The body supplies a defensive tissue reaction which in its turn is devoured by the malignant cells. On the other hand, many, perhaps all, basal-cell tumors, particularly in their beginning, seem to have a definite mutual relationship with their stroma, and this relationship resembles the one normally found in the adnexa. It expresses itself in the polarity, the "palisading" of the outer-cell layer, and in the formation of parallel bundles of fibrous tissue, also in the arrangement of the lattice fibers (Way [41]). Foot [9] found a distribution of nerve fibers in the stroma which resembled the one around hair follicles. The partial differentiation of the epithelium towards hairs, follicular sheath, or glandular type, and the mucinous or hyaline transformation of the stroma also may be viewed as evidence of mutual influences. Basal-cell tumors often are "combination" tumors (I avoid the word mixed tumors), just as in the normal genesis of the adnexa epithelium and stroma form an indivisible whole.

"Organoid" Epithelial Skin Tumors

	Structure Resembling			
Degree of Differentiation	Epidermis	Hair Follicle	Sebaceous Gland	(Apocrine) Sweat Gland
Pure excess	Verrucous nevus	Hair nevus	Sebaceous nevus	Sweat gland nevus
Fairly well differentiated	Verruca senilis	Folliculoma	Sebaceous adenoma	Hidradenoma
Intermediate		Benign Cystic Epitheliomas		
		Trichoepithelioma		Syringoma
Undifferentiated		Basal-Cell Epitheliomas		

It is a great temptation to theorize about the origin and the etiology of tumors, and particularly about that fascinating group which by convention is called, and probably will continue to be called, basal-cell epitheliomas. However, it must not be forgotten that histologic sections from surgical material are open to individualistic interpretation, and that any histogenetic conclusions based on such material necessarily remain tentative and hypothetical. Evidence of experimental nature is urgently needed for clarification of the issues. Meanwhile, it remains the principal task of the dermatopathologist to diagnose tumors, and by correct diagnosis and classification to give the clinician solid ground for proper treatment based on the anticipated course and prognosis of the tumor. In the discussion which has been conducted about the origin of the basal-cell tumors in the past several years, a very important change of classification of a considerable proportion of cutaneous neoplasms has been suggested, which, if proved correct, would have far-reaching practical consequences, but which has not been emphasized by most of the discussers. That change in concept is the abandoning of Darier's classification of the epi-

41. Way, S. C.: Lattice Fibers: Their Diagnostic Value in Epithelioma, Arch. Dermat. & Syph. **16**:25, 1927.

theliomas into typical (squamous-celled), atypical (basal-celled), and metatypical (intermediary and mixed) ones. According to Darier and Ferrand,[42] the latter group constitutes about 15 to 20% of all epitheliomas. It has the radioresistance and potentiality for metastasis of prickle-cell carcinoma and should be treated as such, although it often resembles basal-cell epithelioma clinically and histologically. Montgomery [43] and Jadassohn, through his pupil Juon,[44] concurred with this concept. Montgomery, who preferred the name basal-squamous epithelioma concluded that basal-cell epithelioma may, through metamorphosis, become a basal-squamous cell epithelioma or even a squamous-cell carcinoma. Diagnosis of a mixed basal-squamous carcinoma was founded on the presence of prickle cells and keratinization in a tumor. Foot,[9] who did not mention basal-squamous epitheliomas, probably included them in his pilar type of adnexal carcinoma. According to him, Lever,[16] Lennox and Wells,[45] and Thackray [46] the presence of keratin in a basal-cell epithelioma is not a sign of greater malignancy, but of greater differentiation. It may mean higher radioresistance, but according to this concept it would not mean higher risk of metastasis. Lever doubts the existence of tumors which are intermediary between basal-cell epithelioma and squamous-cell carcinoma, but admits that basal-cell epithelioma, like other chronic lesions, may occasionally stimulate the secondary development of a squamous-cell carcinoma.

A decision between the older and newer concepts will have to await epicritical analysis of the course in a large number of cases. Meanwhile, any feature which in questionable cases can help in the decision of whether an epithelioma, with or without cornification, is of basal-cell or of epidermoid type must be welcome to the dermatopathologist. It is believed that attention paid to the stroma and to the relations between epithelium and stroma can help in the diagnosis in some difficult cases.

SUMMARY

Four cases of unusual fibroepithelial skin tumors are presented which clinically resemble fibromas or papillomas, while their histologic characteristics combine features of the intracanalicular fibroadenoma of the mamma, the reticulated type of verruca senilis, and of superficial basal-cell epithelioma with excessive formation of fibrous stroma. The differences between these tumors and true verruca senilis are discussed, and the development of true basal-cell epithelioma from the epithelium of the benign tumors is suggested.

As it is believed that all epitheliomas of the skin may originate from adult pluripotential cells rather than from one or the other specific part of the epithelial system or from embryonic rests, a descriptive classification of organoid tumors is

42. Darier, J., and Ferrand, M.: L'épithéliome pavimenteux mixte et intermédiaire, Ann. dermat. et syph. **3**:385, 1922.

43. Montgomery, H.: Basal-Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50, 1928; Histogenesis of Basal-Cell Epithelioma, Radiology **25**:8, 1935.

44. Juon, M.: Über die "metatypischen" Formen der Hautepitheliome, Arch. Dermat. u. Syph. **157**:81, 1929.

45. Lennox, B., and Wells, A. L.: Differentiation in the Rodent Ulcer Group of Tumours, Brit. J. Cancer **5**:195, 1951.

46. Thackray, A. C.: Histological Classification of Rodent Ulcers and Its Bearing on Their Prognosis, Brit. J. Cancer **5**:213, 1951.

based on resemblance to, rather than on derivation from, the epidermis or adnexa. Attention is called to the recent tendency to abandon Darier's classification of epitheliomas.

Evidence of or absence of mutual relations between the epithelium and connective tissue is suggested as a possible basic difference between basal-cell epithelioma and epidermoid carcinoma.

ABSTRACT OF DISCUSSION

DR. CARL W. LAYMON, Minneapolis: Dr. Pinkus has devoted a great deal of thought to his interesting subject.

When Dr. Lamb sent me a telegram last week telling me that Dr. Zola Cooper was ill and would be unable to discuss the paper, I was rather confused about the title as it appeared on the program ("Pre-malignant Fibroepitheliomatous Tumors of the Skin"). When I was able to obtain a copy of the paper and noted that the actual title was "Pre-malignant Fibroepithelial Tumors," the confusion decreased to a certain extent, but not entirely.

Certainly the disorder must be an unusual one, since Dr. Pinkus observed only four cases in over 900 epitheliomas which were examined over a period of three years. He was able to find but three other cases in the literature in which there was a similarity either clinically or histologically. As he mentioned in the paper, such cases, in many instances, must have been interpreted in some other way.

Dr. Pinkus stated frankly at the beginning of his paper that he does not believe that these tumors constitute a new entity. The question at once arises then—what old entity do they represent?

According to the author the histologic features appear to be midway between verruca senilis and superficial basal-cell epithelioma. In two of his four cases there were clinical lesions which were characteristic for verruca senilis, basal-cell epithelioma, or both. I think that most of us agree that occasionally basal-cell epithelioma can develop from verruca senilis.

Dr. Montgomery mentioned subepidermal fibrosis. Some dermatopathologists feel that this disorder occasionally can produce enough proliferation of basal cells to simulate the histologic picture of basal-cell epithelioma. Others believe that subepidermal fibrosis and basal-cell epithelioma can coexist side by side.

If the tumors which Dr. Pinkus describes do not constitute a new entity, which he admits, the other possibilities which I have mentioned must be considered. The study of more cases may clarify the problem.

OCCUPATIONAL MELANOSIS

A. J. REICHES, M.D.
ST. LOUIS

DURING World War I Riehl [1] described an interesting pigmentary disturbance with furfuraceous scaling and follicular hyperkeratosis. It may begin as a pruritic erythema which is followed by a light brown or chocolate pigmentation and diffuse and follicular hyperkeratosis. In the early stages there are macular spots of lentil size, which later coalesce. As the condition progresses a distinct bluish-red hyperemia and a diffuse follicular hyperkeratosis develop. The skin has the appearance of having been dusted with a fine flour. Usual distribution is over the forehead, the sides of the face, the backs of the hands, the extensor surfaces of the forearms, the axillary folds, and the legs.

Riehl [1] and his associates [2] reported a total of 18 cases. It is of interest to note that between 1945 and 1948, a period of war disturbances, Arzt,[3] of Vienna, saw 165 cases of this dermatitis. In 1941 Pierine [4] and others [5] reported cases from Argentina, and in 1946 Storck [6] reported six cases from Zurich. Sidi [7] mentioned in a personal communication that cases of occupational melanosis (Riehl's melanosis) have been very frequent in France during and since World War II. Joulia, Le Coulant, L'Epée, and Texier,[8] in 1950, reported the occurrence of 200 cases of the disease in Bordeaux, France. Since very little has appeared on this subject in the American literature, it may be of interest to report four cases of this dermatosis (two in detail) which have been observed in one single group of factory workers.

REPORT OF CASES

CASE 1.—A white woman, aged 40, was first seen with a complaint of itching which had been present for 13 months on the sides of her face and neck and on the back of her hands, forearms, and legs. The itching and roughness began on the hands and within a few days spread to her arms, face, neck, thighs, and legs. She had been employed for 10 years as a machine operator in a can factory. Searching for an occupational irritant, attention became focused on the fact that she used oil on the tin plate from which she stamped can tops.

Read before the Section on Dermatology and Syphilology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 12, 1952.

1. Riehl, G.: Über eigenartige Melanose, Wien. Klin. Wchnschr. **30**:780, 1917.

2. Kerl, W.: Über die "Melanose (Riehl)," Arch. Dermat. u. Syph. **130**:436, 1921.

3. Arzt, L.: Weiterer Beitrag zur "Melanosis Riehl," Wien. klin. Wchnschr. **60**:594, 1948.

4. Pierine, L. C.: Dermatoses pigmentarias de la casa y del cuello, Thesis, Buenos Aires, 1941, p. 115.

5. Orol Arias, C.; Pessano, J., and Radice, J. C.: Melanosis descubiertas durante la guerra (1914-1918): Enfermedad de Riehl-Hoffmann-Habermann; Contribucion a su estudio, Rev. argent. dermatosif. **24**:231, 1940.

6. Storck, H.: Über Riehl'sche Melanose, Dermatologica **92**:246, 1946.

7. Sidi, E.: Personal communication to the author.

8. Joulia, P.; Le Coulant; L'Epée, B., and Texier: Quelques cas de mélanose de Riehl: Étude clinique et histologique, Ann. dermat. et syph. **10**:364, 1950.

Fig. 1 (Case 1).—Lesions of forearms and hands.

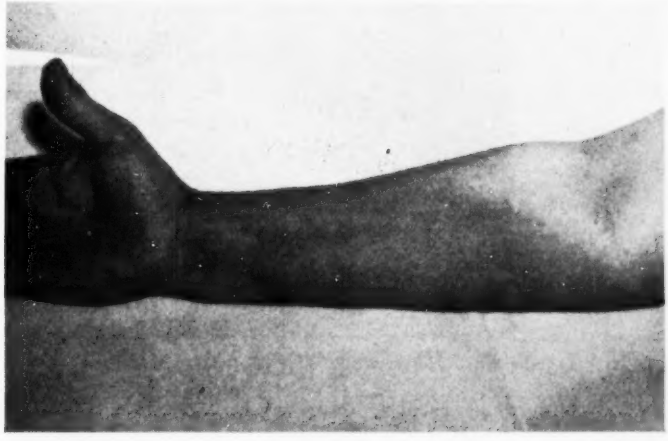

Fig. 2 (Case 1).—Lesions on volar aspect of forearm.

Physical examination showed a well-developed somewhat obese woman. On the extensor surfaces of the proximal phalanges of both hands there was a keratotic plugging of the follicles and a very fine hyperkeratosis extending over the wrists to the upper third of the forearms. The volar aspects of both forearms also showed plugging of the follicles and a diffuse hyper-

Fig. 3 (Case 2).—Pigmentation on back of neck.

Fig. 4 (Case 2).—Pigmentation on sides of neck and forehead.

keratosis, with brownish-red pigmentation. There were bilateral café-au-lait patches and erythematous pigmentation of the face and neck.

Case 2.—A 39-year-old woman, who for 18 months had been working beside the first patient, complained of itching and burning and a discoloration of the skin on the sides and back of her neck, forehead, and the backs of her hands. The dermatitis had started nine months previously on her neck, spreading within a week to her forehead, forearms, and lower legs. There was a

reddish-brown pigmentation on the lateral aspect of her forehead, sides and back of the neck, forearms, and lower legs, accompanied by a bluish-red hyperemia and diffuse follicular hyperkeratosis. She was in excellent health, except for marked varicosities of her right leg.

MICROSCOPIC EXAMINATION

Biopsy of a specimen from the left forearm of the first patient was done. The epidermis showed hyperkeratosis and some atrophy and flattening of the rete pegs. There was a mild degree of liquefaction degeneration of the basel cell layer. The

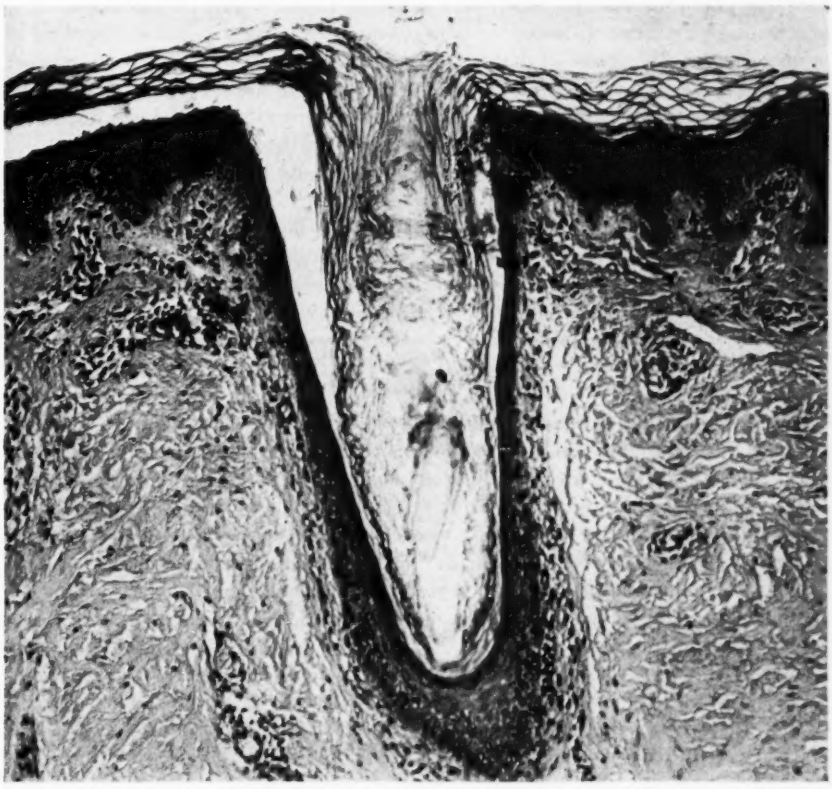

Fig. 5 (Case 1).—Occupational melanosis (Riehl's melanosis).

walls of the follicles were thinned, and the follicles were dilated and filled with keratotic plugs. The upper part of the dermis was edematous and contained dilated blood vessels and a perivascular and perifollicular lymphocytic infiltrate. There was no apparent increase in melanin in the basal layer of epidermis. In the upper part of the dermis there were numerous chromatophores filled with melanin pigmentation. Sections stained for iron pigmentation gave negative results.

DERMATOLOGICAL EXAMINATION

An examination was made of the working conditions of these women. It was found that these two patients, as well as 14 other female employees, used a very

light, pale paraffin oil on the tin plate from which the can tops were stamped. As far as could be ascertained, no change in the type of oil had occurred for many years. Among the group of 16 workers a similar pigmentary disturbance with follicular plugging and a diffuse hyperkeratosis of the forearms and legs was found in two women heretofore not examined. They also complained of severe itching and burning as well as pigmentary disfiguration. The jobs of the patients were changed, and in from three to eight months the pigmentation and follicular plugging disappeared.

A patch test with the oil was applied to the forearm and neck of the first patient after the pigmentation had faded. The test was positive with the development of pruritus and erythema followed by pigmentation. A control patch test applied to my forearm was negative. It took almost six weeks for this reaction to disappear. For reasons beyond my control, the other three patients were not given patch tests.

The refinery reported that the oil with which the patients had come in contact was a "straight" paraffin product with the following specifications:

Gravity*	A. P. I.	28.6
Flash†	F. Min.	330
Pour‡	F. Max.	35
S. U. Viscosity§	at 100 F.	80-85
Color N. P. A.‖		1½-2

* As measured by the American Petroleum Industry measurement. Equal to specific gravity of 0.8838. About 7½ lb. to gallon. Lighter than water.
† Minimum temperature at which vapors of the oil will burn.
‡ Maximum temperature at which it will pour.
§ Number of seconds it takes to pour at 100 F. according to Soybolt 2nd Universal Viscosity.
‖ Standard for measuring color. This means that this is a pale oil.

COMMENT

Arzt [9] and the Viennese group of dermatologists still consider occupational melanosis (Riehl's melanosis) to be caused by nutritional deficiencies, in all probability the result of wartime rations. Riehl [1] and early investigators had attributed this melanosis to the mixture of beans and "ersatz" flour used in Austria during World War I, which they thought formed a skin photosensitizer. More recently, Joulia, Le Coulant, L'Epée, and Texier [8] have felt that their cases of occupational melanosis (Riehl's melanosis) were caused by endocrine and alimentary imbalance. It is interesting that a vitamin A deficiency was suspected in one of my cases, which was quite natural in view of the skin lesions. The family physician had given the patient 200,000 units of vitamin A daily over a period of six months. This therapeutic experiment did not furnish evidence that vitamin A deficiency played a role in this particular instance. Sulzberger and Lazar [10] have reported a case in which they suspected a hypervitaminosis A associated with hypothyroidism rather than an avitaminosis.

In 1918 Hoffmann and Habermann [11] described a clinically similar melanosis caused by tar. Kissmeyer,[12] Kinnear,[13] Pierine,[4] and Orol Arios, Pessano, and

9. Arzt, L.: Personal communication to the author.

10. Sulzberger, M. B., and Lazar, M. P.: Hypervitaminosis A.: Report of a Case in an Adult, J. A. M. A. **146**:788, 1951.

11. Hoffmann, E., and Habermann, R.: Arzneiliche und gewerbliche Dermatosen durch Kriegsersatzmittel (Vaseline, Schmieröl) und eigenartige Melanodermatitiden, Deutsche med. Wchnschr. **44**:261, 1918.

12. Kissmeyer, A.: Über Teer Melanose, Arch. Dermat. u. Syph. **140**:357, 1923.

13. Kinnear, J.: A Case of Riehl's Melanosis, with Notes on the Classification of the Poikilodermas, Brit. J. Dermat. **47**:191, 1935.

Radice,[5] and Storck[6] have described or reported cases of melanosis which they considered to be identical with occupational melanosis (Riehl's melanosis). These authors found hydrocarbon fractions, oils, tars, or greases to be the causative agents. Sidi[7] and his associates have studied many of these cases in Paris and were able to show the importance of local irritants. In most cases these were synthetic essences and mineral oils used as substitutes in cosmetics because of wartime shortages. Sulzberger and Baer[14] have editorially commented that toxic products of hydrocarbons, tars, and oils are often an etiological factor in occupation melanosis (Riehl's melanosis).

Civatte[15] described a pigmentary disturbance which apparently differs from the melanosis of Riehl in that the lesions are limited to the face and neck. He described what he called "pigmented, reticulated poikiloderma," which he and many other observers consider to be identical with occupational melanosis (Riehl's melanosis).

Are we justified in considering these pigmentary dermatoses to be one disease entity? In some cases the etiological role of exogenous irritants has been well established. The four cases here reported are a fair example of this type of occupational melanosis (Riehl's melanosis). However, in North America, in contradistinction to Europe, few, if any, cases have been encountered suggestive of a nutritional or endocrine etiology.

It appears logical to assume that these pigmentary dermatoses are in all probability representatives of an interesting syndrome.

SUMMARY

Four cases of occupational melanosis are herein reported. The question as to whether occupational melanosis (Riehl's melanosis) is a disease entity or a syndrome is discussed.

ABSTRACT OF DISCUSSION

DR. S. BECKER, CHICAGO: Even though Riehl described the disease which bears his name 35 years ago, some of its features are still obscure. He himself was of the opinion that it was caused, at least in part, by exposure to sunlight, a concept that has been echoed by almost all the writers on the subject. Clinically and microscopically, the disorder is identical with sensitization melanosis, which results from photodynamic reaction. If the various substitute foodstuffs had been causative, as believed by Riehl, one could scarcely explain the predominance in women, unless it could be shown that they were exposed to sunlight more than were the men. When externally applied materials are considered, the greater incidence in women could be accounted for by the use of substitute cosmetics, many of which have been incriminated by patch test.

Many men presented a picture identical with that of Riehl's melanosis, but, because they were working in industries, diagnosis was made of melanosis from oil. The clinical pictures differed slightly, because oils tended to produce follicular hyperkeratosis and folliculitis.

Certain features of sensitization melanosis are not sufficiently appreciated. First of all, the offending sensitizer must usually be vigorously rubbed into the skin. This application must be followed soon after by exposure to sunlight. It has been shown repeatedly that it is possible to apply oil of bergamot, a potent sensitizer, so carefully that it merely acts as a filter.

By the time the patient presents herself for treatment, there may already be so much melanin in chromatophores that, regardless of removal of the cause and of the treatment employed, about eight months must elapse before it will be completely absorbed.

Dr. Clinton W. Lane gave aid in the preparation of this paper.

14. Sulzberger, M. B., Editor: 1945 Yearbook of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1946, p. 278.

15. Civatte, A.: Poikilodermie réticulée pigmentaire du visage et du cou, Ann. dermat. et syph. **4**:605, 1923.

PARADOXICAL EFFECT OF PENICILLIN

Epithelioma in Situ Associated with Syphilitic Granuloma

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BROOKLYN

THE FOLLOWING report of a case recently observed is presented as an interesting demonstration of a paradoxical effect of penicillin therapy. The case also suggests the possibility that other paradoxical effects may follow use of some of the newer therapeutic agents.

REPORT OF A CASE

M. M., age 76, was admitted March 15, 1952, with the following history: For the past year, the patient's family had noticed a progressive impairment of his memory, particularly for recent events. This became worse to a point where he began to indicate abnormal behavior. At the same time, he showed weakness of both legs, particularly the right leg, as well as the right upper extremity, with dragging of his right leg and a tendency to fall to the right. There was also a history of having burned his fingers unconsciously on several occasions during this period. There was a loss of bladder control in the past three months. In his personal anamnesis, the only relevant data was a history of a "sore on his penis" about 50 years ago, for which he had received "five or six injections."

Physical examination disclosed three areas of noteworthy abnormality:

1. Central nervous system. The patient showed mental disorientation and euphoria; deep reflexes were hyperactive, with absent superficial reflexes; the Romberg sign was positive, swaying to the right; there was weakened motor function on the right side of the body; there was impaired perception of position in space.

2. Heart. The heart was enlarged, with audible diastolic murmur to the left of the sternum.

3. Skin. There was a lesion on the right buttock (Fig. 1), of which the patient was completely unaware, consisting of an erythematous area irregularly oval, about 5 cm. in diameter, superimposed on which were several areas of crusting and verrucous excrescence. Removal of the lesion showed superficial erosion of the underlying surface; there was some infiltration of the entire lesion to palpation; there were no complaints referable to the lesion.

The serological reaction to the Wassermann test was positive (4+). The VDRL test was positive in 1:32 dilution.

The spinal fluid examination showed no cells, 4+ Wassermann reaction, undiluted; the colloidal gold curve was 000,133,222; total proteins were 60 mg. per 100 cc.

Electroencephalography results were as follows: "Abnormal record with slight electrical disturbance affecting the left frontal area."

X-ray of the skull showed nothing significant.

X-ray of the chest showed enlarged left ventricle and tortuous aorta.

Report of biopsy (Fig. 2) of the lesion done shortly after admission was as follows: "Epidermis is irregularly acanthotic. In one small area it shows a complete disorganization of the

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Attending dermatologist for the Jewish Hospital and Sanitarium for Chronic Diseases.

prickle cells, with variation in size, shape, intensity of stain; there is vacuolization of cells, with several multinucleated elements and marked parakeratosis of the overlying stratum corneum. The corium and underlying cutis showed a much more marked reaction, consisting of numerous discrete and confluent foci of endarteritis, thickened blood vessels, some of which are almost obliterated, surrounded by a dense plasma cell infiltrate."

Because of the marked extent of the inflammatory reaction in the cutis and the minimal degree of involvement of the overlying epidermis, it was felt that the granulomatous reaction

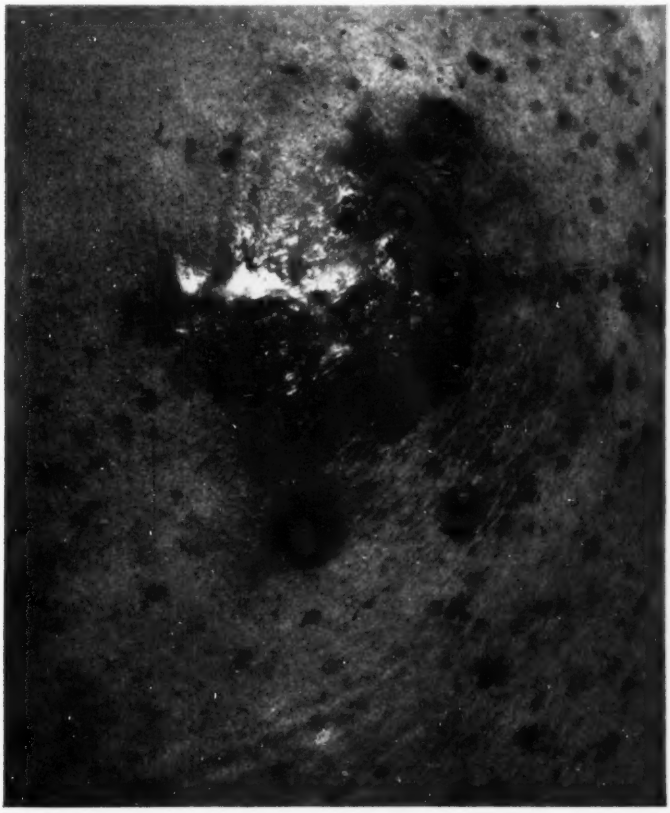

Fig. 1.—Clinical appearance of lesion on admission.

was syphilitic in character. Furthermore, it probably developed prior to the epidermal change (which was interpreted as a Bowenoid in situ type of squamous cell carcinoma), perhaps being responsible for it, or else, if due to primary epidermal neoplasia, the type and degree of reaction were the result of the existence of active syphilis in the patient, as indicated by the central nervous system and cardiovascular involvement.

Accordingly, it was decided to give the patient intensive penicillin therapy, with the object of reducing the syphilitic factor and seeing what side-effect this would have on the epidermal neoplasia, in addition to its possible beneficial effect on the central nervous system and cardiovascular disease. He received over a period of four weeks approximately 25,000,000 units of

penicillin. Actually, a smaller dose had been prescribed, owing to transfer of the patient from an active general hospital to a chronic disease institution, a duplication of therapy took place, before an abstract summary of his prior hospitalization had been received.

There was no clinical change in the appearance of the lesion grossly. His neurological condition showed slight clinical improvement.

Fig. 2.—Low power of first biopsy specimen. Note preponderance of changes in cutis and minimal change in epidermis.

About one month after completion of penicillin therapy the entire lesion was excised and the specimen submitted for histological examination. The picture of the second biopsy specimen disclosed a marked change by comparison with the prior biopsy specimen (Figs. 3 and 4). The report is as follows: "The changes in the epidermis are now quite marked, involving every area of the epidermis seen in several sections, whereas the changes in the corium are minimal and could be interpreted without knowledge of the previous section as a simple nonspecific type of inflammatory reaction to an overlying neoplastic process. However, there is still evidence of some endarteritis and perivascular plasma cells. There are numerous clear perivascular spaces

with dilatation of the vessels, giving the impression that a preexisting lesion of cellular nature has disappeared. Within the epidermis the changes are very marked, classically of the Bowenoid type of dyskeratosis, with marked vacuolization of the individual cells, numerous mitotic and amitotic figures, and considerable variation in size, shape, and tinctorial reaction. In occasional areas there is already definite evidence of invasion into the underlying cutis."

This patient is presented because of the unusual association of an epidermal neoplasm and its possible superimposition on an underyling specific granuloma.

Fig. 3.—Low power of excised lesion.

Whether the granuloma was from its onset a patient-specific reaction to the neoplastic process or whether the neoplasm was a complication of a chronic specific granuloma is difficult to establish in cases of this type. The older literature, contemporary with the pretherapy stage of syphilis, is replete with instances of gummata complicated by epithelioma.

The interesting feature of this case is the rather marked change in the relative degree of the inflammatory versus the neoplastic reactions occurring after penicillin

therapy. Objectively the inflammatory reaction seems to have been almost completely eradicated. The neoplastic element, on the other hand, now seems to have lost all restraint, with cancerization of the entire epidermis and beginning invasion. This might be interpreted as another type of "paradoxical reaction" to specific therapy. Here the restraining effect of an inflammatory reaction, specific in

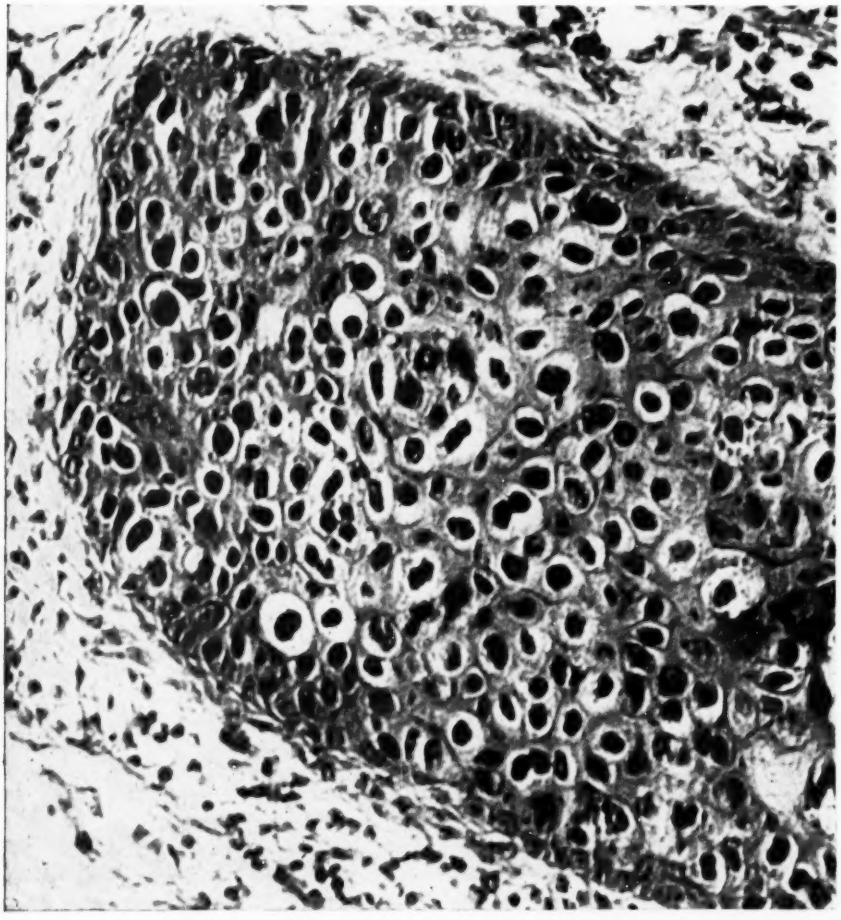

Fig. 4.—High power of epidermis. Note typical changes of Bowenoid epithelioma in situ.

character because of the infected host, but nevertheless restraining histologically, is removed by specific antisyphilitic therapy, allowing freedom of proliferation and invasion by the neoplastic process.

Observations of this type indicate that specific therapeutic agents directed against one disease process may frequently exert remote effects on other processes involved in the dynamic equilibrium of infectious agents, inflammatory and prolif-

erative reactions which characterize the human organism in its relationship to its environment. (Other examples are the increased susceptibility to bacterial infection of patients receiving corticotropin [ACTH] or cortisone; also, the appearance of cutaneous moniliasis after aureomycin and terramycin therapy.) It is tempting to speculate on the implications of such observations; however, that is beyond the province of this report.

SUMMARY

A case of a skin lesion in a known syphilitic associated with clinical evidence of central nervous system and cardiovascular syphilis is presented.

The microscopic examination disclosed histologic features of syphilis and epidermoid carcinoma in situ.

After penicillin therapy the granulomatous reaction subsided, while the neoplastic process became much more extensive.

The possibility of another type of paradoxical reaction is suggested.

135 Eastern Parkway.

Clinical Notes, New Instruments and Techniques

ERYTHEMA INFECTIOSUM

Outbreak in Bristol, Tennessee-Virginia Area

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BRISTOL, TENN.

Since the occurrence of erythema infectiosum has not been reported so far in southeastern United States, the appearance of the disease during the summers of 1949, 1951, and 1952 in the Bristol, Tennessee-Virginia area is reported.

I saw the first two patients with this disease in Johnson City, Tenn., 22 miles (35 km.) from Bristol, in 1949. Between April 7 and Oct. 21, 1951, I saw 24 in Bristol, and between April 19 and Aug. 2, 1952, I saw four. Physicians in the Johnson City area saw several patients with the disease during the summer of 1951.

This report is based on the thirty cases of erythema infectiosum which I saw.

With two possible exceptions, the disease began with red cheeks. This redness varied from a diffuse erythema to closely grouped tiny papules on an erythematous base. It was most intense beneath the eyes, flaring out to either side from the nose, like the single wing of a butterfly, and fading toward the ears. It often felt warm to the touch. The perioral area, the lids, and the chin were, as a rule, uninvolved. In one or two days an eruption appeared in varying extent on the arms, thighs, forearms, buttocks, legs, trunk, and shoulders. It varied from a diffuse mottled erythema to an eruption resembling erythema multiforme. Scarlatiniform, morbilliform, spotted purpuric, urticarial, and, in one instance, bullous lesions were observed. On the buttocks it was frequently urticarial. In from one to several days the redness faded from the cheeks. As it disappeared there was often an erythematous lacework with a faintly cyanotic hue, noted especially on the thighs. The resemblance to serum sickness caused difficulty in the diagnosis of one case, not included, in which antitetanic serum had been administered 10 days before.

Systemic manifestations were absent or mild. One patient looked sick and complained of arthralgia. The others looked well and alert and apparently felt well, in spite of the occasional elevation of body temperature to as high as 101 F.

Penicillin and aureomycin had no effect on two patients. Sulfose (sulfonamide preparation consisting of equal parts of sulfadiazine, sulfamerazine, and sulfamethazine) may have helped one patient, but the evanescence of the rash in many instances makes it difficult to say. Corticosteroids therapy was not tried.

Spotting of cases on a map of Bristol showed that there was no tendency toward grouping. They were confined to older residential areas and were not in any areas of school or church.

Twenty-two of the patients (70%) were 6 years old or younger. There was no significant sex difference. In only two instances were there two cases in the same family. Two adults thought that they had had the disease. All the patients but one were of the Caucasian race. The mother of one of the patients was Hawaiian.

Sixteen patients (over 50%) apparently had pruritus. Insect bites were observed in six patients (20%). In a few instances the disease resembled chicken-mite dermatitis.

Incubation period was not determined. In one red cheeks developed when he was near the North Carolina coast, 16 days after he left Bristol. He may have contracted it there, since in one patient the disease developed in Maryland, before he came to Bristol.

The mother of one patient had been "bitten all over by starling mites," two weeks before erythema infectiosum developed in her son. She destroyed the mites with chlorophenothane (D.D.T.). She thought that her son had also been bitten by the starling mites. Another patient had flea bites. Eradication of the fleas cured her urticaria, but not her erythma infectiosum. Concerning one patient who had several relapses, the father remarked that starlings were unusually prevalent around their house. The previous summer he had destroyed a nest which was full of mites.

In this connection the distribution of cases suggests the presence of nesting birds. Possible exposure to chicken mites was unusual in the case histories. In 1952 the disease developed in one patient who was within 20 yd. (18 meters) of a starling nest and who was less than a 100 yd. (91 meters) away from a patient who had had the disease in 1951. An old starling nest was found nearby. This patient had been given a dead starling with which to play just before the onset of the disease. Also, during the peak year of the outbreak there appeared to be an undue prevalence of insect bites. Starlings were thought to be more abundant at the same time. In 1952 they were very much in evidence early in the season. They were seen only occasionally during the late summer.

SUMMARY

Thirty cases of erythema infectiosum occurring in the Upper East Tennessee-Southwest Virginia area are reported. The disease has appeared during three of the past five summers and may be endemic in the area.

Attention is called to the resemblance of the disease to serum sickness.

A dermatitis due to mites carried by starlings is added to the growing list of dermatoses due to insect bites.

The possible role of the starling in the pathogenesis and transmission of the disease is suggested.

PUNCH BIOPSY WITH AUTOGRAFT

A Cosmetic Office Procedure

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JOHANNESBURG, SOUTH AFRICA

In obtaining punch biopsy specimens of a diameter greater than 2 mm. a visible scar results; this is undesirable when the face or neck are concerned. I have for some time been using the technique here outlined in the management of small growths requiring removal and histological examination and have found it equally useful in the treatment of cosmetic blemishes such as isolated scars of varicella. The method depends on the use of a second excised disc, obtained from the same patient, as an implant.

TECHNIQUE

I have used grafts from various sites, and all eventually prove satisfactory; those from the submammary fold and from behind the ear become indistinguishable in texture most quickly. The procedure is carried out under ordinary procaine anesthesia of both areas.

Owing to retraction of the biopsy wound and contraction of the disc which is to be grafted, it is necessary to cut the latter with a punch whose diameter is 50% greater than that of the removed specimen; thus, a 4 mm. punch excision requires a 6 mm. graft. The biopsy specimen is taken first; as soon as bleeding has been reduced to a slight oozing, the donor graft is excised and implanted immediately. After a few seconds' light pressure with a spatula, a collodion dressing is applied. The donor site is treated in the normal way. The whole grafting operation adds some two minutes to the time normally needed for a biopsy.

Care must be taken that the graft is not deeper than the excised specimen. If this should be the case, tissue may be removed from the under surface of the graft with sharp pointed scissors. Even if the graft protrudes a little after healing, the surface may be lightly sparked with the diathermy needle after a few weeks and an equally satisfactory result obtained.

The collodion dressing is removed with ether after five days, and no further dressing is required. Occasionally the surface of the implant necroses; should this happen I apply further collodion dressings until the black paper-thin membrane separates. Necrosis of this type does not prejudice the result, and after some months it is usually impossible to locate the site of the biopsy excision.

ACNEFORM ERUPTION ON AN INFANT AFTER ANTEPARTUM AND NEONATAL CORTISONE THERAPY

ROBERT CRAFT SMITH, M.D.
JOHN DENT, M.D.
AND
VINCENT DERBES, M.D.
NEW ORLEANS

Many drugs are known to cross the placenta and to exert an influence on the fetus. Cortisone appears to be capable of crossing the placenta, and it has been used in an effort to minimize or prevent the effects of erythroblastosis fetalis. Pregnant Rh-negative women who had previously given birth to erythroblastotic babies were given oral cortisone at about the 28th week of pregnancy.[1] In one instance, it appears that cortisone thus administered might have caused a generalized acneform eruption on a newborn infant. The mother had received 100 mg. of cortisone daily for two months immediately prior to delivery. The infant was given 75 mg. of cortisone the first day and 50 mg. the second. A generalized acneform eruption developed, characterized essentially by the appearance of numerous superficial pustules. The cortisone therapy was discontinued, and penicillin and streptomycin were administered. The eruption disappeared entirely within three or four days. Although the *post hoc* appearance of the rash does not prove that the cortisone was responsible, the well-known tendency of cortisone toward the production of acne, as well as its role in the dissemination of streptococcic and other infections,[2] makes it rather suspect in this instance.

1. Dyer, I.; Dent, J.; Smith, R. C.; Strange, J.; Davenport, J., and Derbes, V.: Use of Cortisone in the Treatment of Erythroblastosis Fetalis, to be published.

2. Thomas, L.: The Effects of Cortisone and Adrenocorticotropic Hormone on Infection, Ann. Rev. Med. **3**:1-25, 1952.

LEUCOPENIA OCCURRING DURING INDUCED MALARIA

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AND
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Leucopenia of varying degree developing during the paroxysms of induced malaria is an expected phenomenon. However, this fact is not generally known and, certainly, has not been widely publicized in recent years. Consequently, when severe leucopenia was discovered in a patient undergoing malarial therapy for central nervous system syphilis, considerable concern and speculation were occasioned. The question arose of whether or not the malaria should be terminated, and if not, what would probably happen?

REPORT OF A CASE

Mrs. L. A., a 44-year-old white woman, was admitted to Ancker Hospital on Sept. 3, 1948. She stated that during the previous six weeks she had experienced some loss of memory for recent events. She complained of inability to concentrate, of headache, and of some visual dis-

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turbance. An informant said that the patient had recently become "sloppy" about her housework and frequently, while preparing meals, allowed food to burn on the stove.

The past history was noncontributory. The patient said she had no knowledge of primary or secondary syphilitic manifestations.

Examination revealed a well-developed, slightly obese, middle-aged white woman whose speech was slow and hesitant. She repeated catch phrases, such as "Methodist Episcopal," well but slowly. She was able to repeat six digits. She was oriented as to time and place. The left pupil was larger than the right, and both reacted sluggishly to light and in accommodation. The findings of the rest of the physical examination, including neurological, were essentially negative.

Results of laboratory examination were as follows: blood Wassermann test, 4+, Kahn, 4+; the findings in the spinal fluid follow: globulin, trace; number of cells, 20 per cubic millimeter (75% lymphocytes, 25% polymorphonuclears); Wassermann reaction, 4+; sugar, 38.2 mg., protein, 65 mg., chloride, 717 mg., per 100 cc.; colloidal gold curve, 55,554,210,000.

The urine was normal. A complete blood cell count showed the following: hemoglobin content, 12.9 gm.; leucocyte count, 8,350 (67% polymorphonuclears, 23% lymphocytes, 6% monocytes, 2% eosinophiles, 2% basophiles); erythrocyte count, 3,740,000. The sedimentation rate was 92 mm. in one hour.

A diagnosis of early paresis was made. After three preparatory injections of bismuth, the patient was inoculated on Sept. 24 with 10 cc. of quartan malaria blood. Her first paroxysm occurred on Sept. 30. On the same day penicillin administration in a dosage of 80,000 units every three hours, was started. On Oct. 1 a blood cell count revealed the following: hemoglobin content, 11.2 gm.; erythrocyte count, 4,530,000; leucocyte count, 1,700. A repeat leucocyte count showed 1,450 cells per cubic millimeter, with the following differential distribution: 61% polymorphonuclears, 25% lymphocytes, 9% eosinophiles, 5% undifferentiated. It was at this point that conferences were held to determine whether or not the malaria should be terminated. It was decided that no attempt be made to terminate the malaria at this time. However, 500 cc. of whole blood was given intravenously. On the following day (Oct. 2) the leucocyte count was 2,100, with 92% polymorphonuclear cells (many toxic forms), 4% lymphocytes, and 4% monocytes. On Oct. 4 the leucocyte count was 2,850, on Oct. 6 3,700, and on Oct. 8 4,350, with 88% polymorphonuclear cells (many toxic forms), 8% lymphocytes, and 4% monocytes. Thereafter, although the leucocyte count fluctuated, the percentage of lymphocytes in the differential smears continued to rise to normal levels. The malaria was terminated with quinine administration on Oct. 15, after the patient had had a total of 10 paroxysms and a temperature of above 103 F. for 37 hours. The total dose of penicillin administered was 8,000,000 units. At the time of discharge, on Oct. 25, the blood cell count was as follows: hemoglobin content, 9.9 gm.; erythrocyte count, 3,920,000; leucocyte count, 4,700 (66% polymorphonuclears, 30% lymphocytes, 4% monocytes.)

COMMENT

It is the purpose of this presentation to recall past studies which adequately demonstrated that induced malaria, during its incubation period, produces a fall in the total leucocyte count. In the case presented unfamiliarity with this phenomenon led to unnecessary confusion and concern.

Schilling,[1] Winfield,[2] and, later, Doan and Hargraves[3] showed that a marked leucopenia develops early in the course of induced malaria. The polymorphonuclear cells are markedly shifted to the left. The lymphocytes are depressed, as are also the monocytes. During the recovery phase 30 to 40% of the leucocytes may be monocytes. The blood picture in inoculation malaria differs materially from that in clinical malaria, in which a leucocytosis is the rule.[5] Likewise,

1. Schilling, V., and others: Malaria Treatment of General Paralysis, Ztschr. klin. Med. **100**:742-776, 1924.

2. Winfield, G. A.: Study of White and Differential Counts in Six Unselected Cases of Inoculation Malaria, J. Lab. & Clin. Med. **17**:985-992 (July) 1932.

3. Doan, C. A., and Hargraves, M. M.: Fever Therapy: Its Indications and Its Limitations, Hospitals **10**:88-92 (June) 1936.

hyperpyrexia induced by hypertherm cabinets is usually associated with a leucocytosis of 10,000 to 60,000 cells per cubic millimeter.[3]

Modern textbooks on syphilology have not failed to retain this information. Moore [4] refers to the work of Schilling and Winfield, while Stokes [5] refers to that of Doan and Hargraves. So far as we have been able to discern, there have been no more recent studies or reports on the subject. As a result, the depression of the leucocyte count during induced malaria is usually unnoticed, while the attention is directed, and justifiably so, to the hemoglobin determinations and erythrocyte counts. It is only when the leukocyte count reaches alarmingly low levels, as in the case presented, that this known phenomenon is recalled.

SUMMARY

A case of induced malaria is presented in which a leucopenia of 1,450 cells per cubic millimeter was observed. It is pointed out that leucopenia, usually less severe than in the case presented, developing during the course of induced malaria is a well described yet unfamiliar phenomenon.

4. Moore, J. E., and others: The Modern Treatment of Syphilis, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 382.

5. Stokes, J. H.; Beerman, H., and Ingraham, N. R.: Modern Clinical Syphilology: Diagnosis, Treatment, Case Study, Ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 156.

MUSHROOM DERMATITIS

Report of a Case

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E. A. W., a healthy white man of 40, complained on March 11, 1952, of an itching eruption on his hands and eyelids. For about one year he had been working in a mushroom plant where mushrooms are grown commercially. The mushroom grown in this plant is the Agaricus campestris, the only mushroom of commercial importance grown in the United States. His job consisted of working the beds, picking the mushrooms and packing them in baskets. The manner in which he used his hands to pick and pack proved to be the key to the correct diagnosis, in spite of, as will be shown, a very misleading history.

Four months prior to the first examination he had picked mushrooms in a room which had been heavily and profusely dusted with an insecticide powder said to contain a nicotine compound. Four days after this exposure, blisters appeared on the pads of the fingers and thumb of the left hand, which he invariably used to pluck the mushrooms, and on the pad of the right thumb, upon which impinged the cutting edge of a short knife used to cut off the root of each mushroom before placing it in a basket. It was obvious that the eruption appeared first on those skin surfaces which were constantly most intimately exposed to the mushroom or to some extraneous coating on the mushroom. The eruption persisted, and in a few days the patient's eyelids became swollen and inflamed. The patient, according to his subsequent story, was convinced that the condition was caused by exposure to the insecticide. He continued to work, but in two weeks was forced to stop because of the severity of the inflammation on his hands and eyelids. At the expiration of two more weeks, he had greatly improved, only to relapse into his former state after returning to work. In spite of local treatment the dermatitis persisted, with partial remissions and exacerbations, until first seen on March 11.

On that date, the patient presented a severe vesiculosquamous dermatitis of all the finger pads of the left hand and the thumb pads of both hands. The eyelids were swollen, erythematous, and scaly. The history and distribution of the eruption immediately indicated that it was caused by contact with either the mushroom or the insecticide, and that the eyelid involvement

was due to the same contactant transferred to the eyelids by the fingers. Patch tests proved that the contactant responsible for all the trouble was the mushroom itself. Three patch tests were applied: mushroom, mushroom dusted with the insecticide, and the insecticide alone. The latter produced no reaction on the skin, whereas both pieces of mushroom produced equally violent positive reactions.

The patient was removed from all contact with mushrooms, boric acid solution compresses were applied, and within seven days return of the affected parts to normal was almost complete.

QUINACRINE (ATABRINE) HYDROCHLORIDE IN TREATMENT OF DISCOID LUPUS ERYTHEMATOSUS

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LOUIS A. BRUNSTING, M.D.
AND
ROBERT R. KIERLAND, M.D.
ROCHESTER, MINN.

Encouraged by the report of Page,[1] we started the treatment of lupus erythematosus with quinacrine (Atabrine) hydrochloride in January, 1952. This paper is a report of our experience to date.

Page at the time of his report had treated 18 patients with lupus erythematosus, and only 1 failed to exhibit improvement. The dosage suggested was 300 mg. of quinacrine hydrochloride administered daily until the skin was stained, and then 100 mg. given daily as a maintenance dose. He stated further that the duration of treatment varied with the clinical response and the degree of discoloration of the skin. In some cases treatment for six weeks was sufficient, and seldom was treatment required for more than three months. He also felt that the degree of improvement was related to the degree of staining of the skin. Page noted dramatic improvement in one case of acute disseminated lupus erythematosus, and the symptoms of rheumatoid arthritis in two other cases of chronic discoid lupus erythematosus subsided rapidly. Page reported that administration of the drug caused a reaction in only one case. This consisted of a generalized hyperkeratosis which affected mainly the upper extremities and was associated with intense irritation. This reaction was not lichenoid in character.

Our personal experience with quinacrine in the treatment of lupus erythematosus covers the year 1952, in which we have treated approximately 40 patients with this drug. In general, our experience is similar to that of Page. In certain cases the results were truly dramatic, especially in those cases in which scarring was pronounced. While the scarring itself was not affected, the evidence of new lesions of lupus erythematosus tapered off within a few weeks. It should be remembered that the great majority of the patients in previous years had undergone many types of treatment without benefit.

We feel that 40% of our patients obtained excellent results, 35% obtained moderate benefit, while 25% did not obtain any benefit or became worse.

In the group that did not obtain any benefit or became worse were four cases in which large areas of the body were covered with active lesions of lupus erythematosus. The laboratory findings were abnormal in these cases. After the administration of quinacrine, increased activity of the affected portion of the skin developed, together with a diffuse superficial scaly erythema which subsided slowly after the administration of the drug was discontinued. A lichenoid reac-

From the Section of Dermatology and Syphilology, Mayo Clinic.

Read at the Eleventh Annual Meeting of the American Academy of Dermatology and Syphilology, Chicago, Dec. 11, 1952.

1. Page, F.: Treatment of Lupus Erythematosus with Mepacrine, Lancet **2**:755-758 (Oct. 27) 1951.

tion simulating lichen planus developed in one case, and fever occurred in another case. In other words, our beneficial results have been observed only in cases of chronic discoid lupus erythematosus without systemic repercussions. The best results have occurred in cases in which there have been but few active plaques with scarring in the exposed areas of the skin.

Untoward reactions have been seen only in the patients just mentioned, but as we and others use this preparation more we should be aware of the experiences with quinacrine in World War II. While the incidence of untoward reactions to the administration of quinacrine is low, they may be serious and appear rapidly. Particularly prominent are those involving the skin and hemopoietic system. On the skin, drug eruptions simulating lichen planus, eczematoid dermatitis, pityriasis rosa, hyperkeratosis, and exfoliative dermatitis are seen, while fatal aplastic anemia and agranulocytosis sometimes result from suppression of the hemopoietic system. Untoward reactions may also involve the liver, gastrointestinal tract, and central nervous system. Untoward reactions to quinacrine are similar to those resulting from arsenic, gold, and bismuth, which have been used for many years in the treatment of lupus erythematosus.

We believe that quinacrine should be administered only in cases of chronic discoid lupus erythematosus. Evidence of dissemination either on the skin or from the laboratory offers a contraindication to the use of the drug.

Page indicated that beneficial results appear only with the yellowish staining of the skin. We have not found this to be true in all instances, since several patients have had dramatic remissions although their skin has not been stained noticeably by quinacrine.

At present, we are attempting to establish the dosage of quinacrine hydrochloride in an endeavor to determine the length of time the drug should be administered, whether or not repeated short courses of the drug should be used, or whether small maintenance doses given over longer periods are preferable. The doses we have employed thus far have varied from one to four tablets (100 to 400 mg.) per day. It is evident that the requirements of individual patients are variable, as small doses are effective in some cases, while administration of 400 mg. a day has been necessary to produce satisfactory therapeutic results in other cases.

In summary, we feel that the experience of Page has been confirmed. The treatment of chronic discoid lupus erythematosus with quinacrine (Atabrine) hydrochloride is a significant advance. Our early results indicate that such therapy produces the best results in the patient with but few lesions on the exposed areas of the body. Untoward reactions thus far have appeared only in cases of widespread cutaneous lesions and in cases in which laboratory examination has disclosed evidence of systemic involvement. The mechanism of action of the drug is still undetermined.

TOPICAL THERAPY IN MILIARIA RUBRA

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WASHINGTON, PA.

Since World War II there has been considerable investigative effort expended in the study of miliaria rubra, particularly in study regarding its histogenesis. Relatively little has been suggested as regards its therapy. A natural hesitancy accompanies the recommendation of a single local therapeutic agent for the therapy of any dermatosis, but I believe that the proved efficacy of the treatment described justifies this brief report.

In the early part of 1945, during intensive preinvasion maneuvers of a Marine division on Guadalcanal, approximately 150 cases of extensive miliaria rubra were encountered. Twenty of the patients required temporary hospitalization and the majority of the patients were incapacitated. In an effort to find an effective local application it was discovered that 4% tannic acid in 60% alcohol produced surprisingly rapid improvement. The solution was applied twice daily, allowed to dry, and then talcum powder was applied. The only disadvantage encountered was a brownish staining of the overlying clothing. In several cases of unusually severe miliaria rubra a 4% aqueous solution of tannic acid was employed until the eruption became less acute.

From the Pittsburgh Skin and Cancer Foundation.

The use of this preparation was reported by me in 1945 [1] and was subsequently described at an informal meeting of dermatologists at Guam.

Employment of the treatment in civilian practice has fully confirmed its usefulness. In infants 1 or 2% tannic acid in either water or 20% alcohol has worked well.

The rationale of the treatment is admittedly obscure, although tannic acid has recently been recommended as an astringent in hyperhidrosis.[2]

1. Shelton, J. M.: Miliaria Rubra in the Tropics, U. S. Nav. M. Bull. **44**:876, 1945.

2. Herrmann, F., and Sulzberger, M. B.: Some Aspects of Therapy of Sweat Disturbances, A. M. A. Arch. Dermat. & Syph. **66**:162, 1952.

CHLORAMPHENICOL IN TREATMENT OF PRIMARY HERPETIC STOMATITIS AND HERPES LABIALIS

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JACK BUDOWSKY, D.D.S.
HERBERT F. SILVERS, D.D.S.
AND
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NEW YORK

Acute primary herpetic stomatitis [1] and herpes labialis,[1e] oral manifestations of herpes simplex infection, have been described in detail by many investigators. Since chloramphenicol has one of the widest antiviral spectra of the available antibiotics, we attempted systemic chloramphenicol therapy of these diseases.

METHODS

Fourteen patients, 8 males and 6 females, aged 1½ to 28, with primary acute herpetic stomatitis were studied. Chloramphenicol was administered to seven patients, 500 mg. perorally four times a day, for seven days following the making of the diagnosis. In each case use of all other medications was discontinued. The control group of seven patients had remained untreated except for topical palliative therapy. On alternate days each patient was evaluated as to subjective comments, inflammation, lymphadenopathy, infection, swelling, pain, soreness, and reactions to therapy.

Seventeen patients (6 males and 11 females, aged 10 to 58) with herpes labialis were also studied. Chloramphenicol was administered to eight patients, 500 mg. four times a day, for seven days following the appearance of lesions. Nine patients with similar disease but untreated consti-

From the Divisions of Oral Diagnosis and Research (Hannah and Harry Posner Research Laboratory) School of Dental and Oral Surgery of the Faculty of Medicine, Columbia University.

Chloramphenicol (Chloromycetin) for this study was supplied by Parke, Davis & Company, Detroit, through the courtesy of Dr. R. J. Buckman.

1. (*a*) Dodd, K.; Johnston, L. M., and Buddingh, G.: Herpetic Stomatitis, J. Pediat. **12**:95, 1938. (*b*) Burnet, F. M., and Williams, S. W.: Herpes Simplex: New Point of View, M. J. Australia **1**:637, 1939. (*c*) Scott, T. F.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis, J. A. M. A. **117**:999, 1941. (*d*) Ziskin, D. E., and Holden, M.: Acute Herpetic Gingivostomatitis: Report of 15 Cases, J. Am. Dent. A. **30**:1697, 1943. (*e*) Thoma, K. H.: Oral Pathology: A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth, St. Louis, C. V. Mosby Company, 1950.

tuted a control group. Patients were seen every two days and were evaluated as described previously. All other therapy was discontinued. Only patients presenting within three days of the onset of lesions were studied.

RESULTS

On the basis of the expected untreated course and the course of the control group, it is judged that two of the seven patients with primary herpetic stomatitis treated with chloramphenicol showed amelioration of existing symptoms and one showed slight clinical improvement during therapy. However, the response was not dramatic, and the benefits were suggestive of decreased secondary infection. The duration and clinical course of the disease appeared relatively unchanged (approximately nine days for each group).

The course of patients with herpes labialis treated with chloramphenicol did not differ from that of the control group as to the duration, severity, number of lesions, and subjective symptoms. Whereas in one patient in the control group a severe purulent infection complicated the herpes labialis lesions and delayed healing approximately seven days, secondary infection did not occur in any of the chloramphenicol-treated patients. Crusting took place at approximately the same time in the two groups, and final healing occurred on the average in approximately 8½ days in the chloramphenicol-treated group and 10 days in the untreated group (including the patient with severe secondary infection).

In an effort to determine the efficacy of chloramphenicol in preventing recurrences of herpes labialis, chloramphenicol, 500 mg. four times a day for three days, was administered to the treated group three weeks following the complete healing of the herpes labialis lesions. Recurrences of herpes labialis have been noted over a period of one year in five out of eight patients in the chloramphenicol-treated group and in four of the nine patients in the untreated control group.

Reactions to chloramphenicol included nausea in two patients and diarrhea with pruritus ani in one patient.

SUMMARY

The course of acute primary herpetic stomatitis and herpes labialis is relatively unchanged by chloramphenicol therapy except probably for a decrease in the incidence and severity of superimposed secondary infection.

630 W. 168th St.

Society Transactions

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Harold C. Fishman, M.D., *President*

Stanton B. May, M.D., *Vice-President*

Fred F. Feldman, M.D., *Secretary*

Oct. 28, 1952

Parapsoriasis en Plaques (Brocq). Presented by Dr. Edward L. Murphy.

A. Y. is a 61-year-old white woman of Danish ancestry, born in England. The original lesions began on the medial surface of the right thigh in the summer of 1950. No additional lesions appeared until May 1, 1951. The eruption began as red blotches, covering a palm-sized area made up of about a dozen individual areas just below the umbilicus. These lesions spread laterally from the midline on each side in the succeeding months. In July, 1952, areas over the lower trunk, breast, upper abdomen, lower back, and on the left thigh medially became involved. After the appearance of lesions there is no tendency for spontaneous involution. There is considerable itching, but not much tendency toward scratching. The patient has been in good health. There have been no previous dermatoses.

The eruption consists of salmon-colored macules, approximately 1 to 2 cm. in width, and up to 3 cm. in length, with very faint elevation of some lesions and with some lesions irregularly ovoid to linear. There is a very slight scale, and the long axes of the lesions occur in planes of cleavage to a considerable degree. The skin is thin, and there is apparent atrophy in some of the lesions.

Laboratory studies, including complete blood cell count, sedimentation rate, and routine urinalysis, showed normal findings, except for a moderate secondary anemia of the macrocytic type.

The findings of a biopsy were reported by Dr. Wilbur Sachs:

"Throughout the upper cutis are dilated blood vessels and some interstitial edema. There is a focal and diffuse reaction of small round and wandering connective tissue cells. The epidermis is thin and shows no significant changes. The basal cell margin in some areas is washed out, and there are some inflammatory cells within the epidermis. There are a few small patches of parakeratosis. The acid-fast stain does not reveal the presence of organisms."

DISCUSSION

Dr. Herbert A. Fishbein: I would suggest therapy as outlined by Orlando Canizares at the Veterans' Hospital in New York. Briefly, it consists of calciferol treatment in a dose of 100,000 to 150,000 units daily, together with ultraviolet irradiation.

Dr. Eliot Wolk: A report on the use of vitamin K in the treatment of lichen ruber planus and pityriasis lichenoides chronica with good clinical results appeared in the *Acta dermato-venereologica* (**31**:52, 1951). I have not had occasion to use this treatment.

Dr. Ernest Thomas Fox: I have had three patients with parapsoriasis who were treated both by the administration of vitamin K orally and parenterally and simultaneously by the application of coal tar ointments or lotions to the individual lesions, and who also received generalized irradiation with ultraviolet light. The vitamin K is administered in 10-mg. doses by injection once or twice weekly; 5 mg. tablets three times daily are taken after each meal. The value of these procedures is not yet established, but certainly all three patients have responded favorably to this therapy.

One of these patients has had two relapses, but with more treatment his dermatosis again improved.

DR. STANTON B. MAY: I should like to ask Dr. Fox whether he or other members have used vitamin K in lichen planus with any favorable results. I have tried this therapy (there is an article from Scandinavia that extols this treatment), but I have not had successful results.

DR. HAROLD C. FISHMAN: I would suggest that this is not parapsoriasis. I think that this patient has angioma serpiginosum, for the following reasons. I saw no scale whatsoever. None of the lesions seemed papular to me; none of them seemed scaly to me, and there was a suggestion of atrophy. Histologically, all that I saw was a rather normal type of epidermis, with the exception that there was in certain places a slight disorganization of the basal cell membrane, and that high up in the cutis there was a moderate amount of edema, and also a little bit of perivascular small round-cell infiltration. That is not my conception of parapsoriasis, but it seems to indicate angioma serpiginosum.

DR. EDWARD MURPHY: I did not mean to lead you astray in the matter of the scale. I mentioned that the scale was very slight. In the beginning there was a little more scale than you saw tonight. The patient has had no local treatment, however.

As to the diagnosis of angioma serpiginosum, these lesions, once they develop, remain; they do not undergo involution, they do not change their character in any way, and in angioma serpiginosum the character of the eruption is a changing one in which there are new areas involved, and in which old ones undergo involution. Furthermore, the lesions are characterized by minute punctate peripherally spreading macules.

I think that the diagnosis of parapsoriasis has to be made, because these lesions developed very slowly, and as new lesions develop they retain their original characteristics. They had a very faint but definite scale. They itched a little, but not markedly. None of these lesions are infiltrated.

As to the eventual development of mycosis fungoides in this particular patient, I do not think that anyone can say definitely that it will not occur. My own feeling is that parapsoriasis is parapsoriasis, and mycosis fungoides of en plaque type is mycosis fungoides from the beginning, and that they do not change from one type into the other, despite observations to the contrary.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. HAROLD PRICE.

Mrs. V. S., aged 42, presents lesions on both legs of one year's duration. The lesions are asymptomatic, except for occasional itching. There has been a slow, gradual increase in size, and recently a few new lesions have appeared. There is no personal or familial tuberculosis or diabetes.

Examination reveals that on both shins there are a number of coin-sized patches which are annular or configurate in shape. The center is slightly depressed, with the surface smooth, thinned, and somewhat waxy in appearance. The color is pinkish, with fine telangiectasia. Each lesion is sharply defined by an elevated pinkish infiltrated border.

Urinalysis gave normal results; there was no sugar; a glucose-tolerance test showed a normal curve.

Tissue section shows on hematoxylin-eosin stain foci of homogenization of connective tissue. Within these areas and about them there is an infiltrate of round cells and histiocytes and plasma cells. The blood vessels are thickened, and some show actual occlusion of the lumen. A perivascular infiltrate is also present. The fat stain shows masses of fatty globules and granules in the corium.

Cortisone ointment was applied to lesions on the left leg for only one month, with not much change. Solid CO_2 was applied to a few lesions on both legs, with some improvement. The patient is now taking mixed tocopherols, 50 mg. three times a day.

DISCUSSION

DR. FRED F. FELDMAN: My experience in five cases of necrosis with the use of cortisone ointment has been good. Two cases have been completely cleared with its use. The patient presented tonight apparently has not been helped too much by the cortisone ointment. I asked her about the application, and I do not think that she massaged the ointment in as well as she could

have. I think that it would be worth while to have her repeat the administration of the cortisone ointment in a minimal dose of 25 mg. per gram, a control area again being used. She should spend three minutes' time massaging the cortisone (Cortone) into the areas involved.

DR. FRED F. FELDMAN: Supposedly, ulceration in necrobiosis is rare, but I had the opportunity to see three such patients recently, and in every case the ulcers healed during the use of cortisone ointment, without any change in diet or insulin dosage.

DR. HAROLD PRICE: This patient does not have diabetes. Her glucose tolerance is normal, and from her history apparently none of her parents or grandparents ever have had diabetes. In a query to *J. A. M. A.*, the editor was questioned on the chances of a child's getting diabetes if the parents do not have diabetes, if the father alone has diabetes, or if the mother alone has diabetes. The answer is as follows: If neither parent has been identified as a carrier or as a potential diabetic, the chances of a child's getting diabetes are zero, theoretically. If the parents do not have diabetes but are identified in each instance as a carrier, that is to say, the child of a diabetic, the chances that diabetes will develop in their child are one in four.

If each parent is the child of two diabetics they must be identified as potential diabetics, and the chance that the disease will develop in their offspring is 100%. Apparently, diabetes occurs along Mendelian ratios, of the recessive type. The question that comes up in this condition is this: Do all these patients eventually get diabetes or show manifestations of latent diabetes? In other words, do they show an abnormal sugar metabolism sometime in their life? There is no doubt that many of these cases of necrobiosis occur in manifest or latent diabetics. However, is it possible that there are cases which occur in persons who are not diabetic and who will never become diabetic? I do not believe that we have an answer to that question as yet.

Secondly, another question to be answered is this: Are there two types of necrobiosis? Is there a diabetic type and is there a type which is nondiabetic? I think that also has to be answered.

Lichen Sclerosis et Atrophicus with Bullous Formation. Presented by DR. ANITA GELBER.
Parapsoriasis? Angioma Serpiginosum of Hutchinson? Presented by DR. HAROLD C. FISHMAN.
Atypically Located (Arms) Accessory Breasts (Pseudomamma Type); Other Aberrant Breast Tissue? Presented by DR. JOHN W. CARNEY.
Hemangioma, Cavernous. Presented by DR. STANTON B. MAY.
Arthropathic Psoriasis. Presented by DR. STANTON B. MAY.

PHILADELPHIA DERMATOLOGICAL SOCIETY

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Oct. 17, 1952

Kaposi's Sarcoma. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. MIRIAM REED.

J. B., a white woman aged 70, presented hard-walled bullae with piled-up lichenified borders, isolated as well as in groups, over the front of the feet and the ankles. A raised infiltrated plaque over the toe appeared to be filled with fluid. There were hypertrophic white scaly lichenified patches on the sides of the ankles and small atrophic papules up the side of the leg, and there was ecchymosis on the sides of the hands and wrists. The patient had had "varicose eczema" for years, which was treated at the Skin and Cancer Hospital with x-rays and local measures. About two years ago swelling appeared in the lower part of the leg, not associated with exudation. No new lesions have appeared, and no old ones have healed. The patient was examined by the medical consultant, who found hypertensive heart disease with auricular fibrillation. There was no clinical evidence of systemic involvement by Kaposi's sarcoma.

A complete blood cell count revealed 12.6 gm. hemoglobin content, 4,250,000 erythrocytes, 10,000 leucocytes, 75% polymorphonuclear leucocytes, 23% lymphocytes, 2% eosinophiles. The serologic reactions for syphilis were negative.

The report on the biopsy specimen was as follows, "vascular lesion, possible Kaposi's sarcoma."

The patient has been treated with penicillin, 600,000 units, three times a week for three weeks.

DISCUSSION

DR. M. H. SAMITZ: These bullous-like lesions are not uncommon in Kaposi's sarcoma. MacKee and Cipollaro (*Am. J. Cancer* **26**:1 [Jan.] 1936) described this type of lesion. These are not bullae but real lymphagiomas. An unusual feature here is the occurrence of this disease in a woman.

DR. BERTRAM SHAFFER: I was unaware of the fact that so-called cystic lesions existed in Kaposi's sarcoma until I looked up literature. These are not bullae but lymphangiectatic lesions.

DR. FRED D. WEIDMAN: I agree that they are lymphangiomatous. What is singular is that all the lesions are of that character. I could not see anything hemorrhagic nor hyperkeratotic, and there was not much pigmentation. Usually, over the tumors of Kaposi's sarcoma there is hyperkeratosis, sometimes even verrucosity. I wonder whether the histology of this case would not be more that of lymphangiosarcoma than that of Kaposi's sarcoma. Kaposi's sarcoma has the histology more or less of hemangioendothelioma. I think that in a case of this sort we ought to recognize an entirely separate and distinct type and call it the lymphangiomatous type of Kaposi's sarcoma. On the other hand, what are the objections to calling it lymphangioma—not circumscriptum, but simply lymphangioma?

DR. HERMAN BEERMAN: In this particular case Dr. Weidman made the diagnosis of Kaposi's sarcoma. My diagnosis was vascular disease. This disease does occur in women.

Sarcoidosis Apparently Cured by Quinacrine (Atabrine) Hydrochloride. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. MILTON M. CAHN and DR. EDWIN J. LEVY.

M. McC., a white woman aged 51, was given quinacrine (Atabrine) hydrochloride, 100 mg. three times daily, beginning July 14, 1952. Pigmentation was still present at the site of the lesions on Sept. 27, 1952, but induration has completely disappeared, and the skin is normal to the touch. There are no new lesions. The patient was definitely more comfortable during the last summer. She had no pruritus or any of the other symptoms which she had experienced during the past years. She is now taking quinacrine hydrochloride, 100 mg. a day.

The condition started in July, 1951, each lesion beginning as a small pruritic nodule which gradually became diffuse to form an annular lesion. The results of physical examination were essentially negative. The only medication taken in the past five years has been magnesia magma U. S. P. (milk of magnesia) and, rarely, an acetylsalicylic acid (Aspirin) tablet.

The complete blood cell count showed normal findings. Total protein was 8%, albumin 4.1%, globulin 3.9%. The sedimentation rate was 25 mm. The blood sugar, two hours after meals, was 112 mg. per 100 cc. An x-ray of the chest showed increased hilar markings; x-rays of the hands gave normal findings.

The diagnosis on the biopsy specimen was that of sarcoidosis.

DISCUSSION

DR. JAMES M. FLOOD, Sayre, Pa.: We had considerable experience with quinacrine hydrochloride in India, and the incidence of reaction is probably higher than is generally reported. Apparently there were reactions present in 2 or 3% of the patients in India receiving quinacrine hydrochloride treatment. A small number of these patients showed liver damage. We saw several patients who died of yellow atrophy of the liver, presumably as a result of the use of quinacrine hydrochloride. The cutaneous cases (atypical lichen planus) which we studied with liver function tests showed two results: In some of the older persons a diabetic type of glucose tolerance curve developed, with decrease in serum proteins, and the results of other liver function tests like the sulfobromophthalein (Bromsulphalein) sodium and flocculation tests were positive. Another group had the flat type of glucose tolerance curve and blood sugar which did not rise after administration of epinephrine (Adrenalin). These patients were studied by the internists, and they were certain that some liver damage had occurred. Patients usually had to take quinacrine hydrochloride weeks before a dermatitis developed. Many had lesions that looked like pityriasis rosea at the onset; others had lesions which were eczematous, but in all lichen-planus-like lesions eventually developed.

DR. ISADORE ZUGERMAN: It is my understanding that quinacrine hydrochloride will cause atrophy of the sweat glands, a permanent condition, and with the use of this drug we may cure one disease and cause another. I think that it should be used with caution.

DR. FRED D. WEIDMAN: How many hundreds of thousands of soldiers, sailors, and marines have been treated with quinacrine hydrochloride, and in these hundreds of thousands, how many cases of liver disease occurred?

CAPTAIN WILLIAM M. NEW (MC), U. S. N.: At the time that it was decided that there was liver damage, we had not examined the transfusion jaundice question thoroughly. I believe that a lot of liver damage could be attributed to the diet deficiencies which occur in the tropics under battle conditions.

DR. HARVEY BLANK: Page was the first to report on the use of quinacrine hydrochloride in lupus erythematosus (*Lancet* **2**:755, 1951). The experience of the British physicians has convinced them that it is the most effective drug in discoid lupus erythematosus. In several patients, however, atypical lichen planus has developed as a result of the quinacrine hydrochloride therapy as the lupus erythematosus was subsiding. In our wartime experience I believe that atrophy of the sweat glands occurred only in those patients in whom dermatitis developed as a result of quinacrine hydrochloride therapy. An interesting report by Freedman and Bach has recently appeared in *Lancet* (**2**:321 [Aug. 16] 1952), which describes 23 patients with rheumatoid arthritis, all but one of whom seemed to have been regularly benefited by quinacrine hydrochloride. In some patients the results appeared to be superior to the results obtained with cortisone therapy. Patients with sarcoid are sometimes benefited by cortisone therapy, as are patients with arthritis, and in this patient quinacrine hydrochloride seems to be having a similar effect. The mechanism is obscure.

DR. JAMES M. FLOOD, Sayre, Pa.: I have seen patients who have had their dermatosis for only a few days, and, despite the discontinuance of the quinacrine hydrochloride therapy, the disease progressed to a generalized acute exfoliative dermatitis. I think that this drug should be handled very carefully in treating patients with lupus erythematosus.

Madura Foot Due to Nocardia Asteroides. Presented by DR. E. DELAMATER and DR. J. S. STRAUSS (by invitation).

Congenital Ectodermal Dysplasia (Three Siblings). Presented by DR. MEYER L. NIEDELMAN.

von Recklinghausen's Disease Associated with Optic Atrophy. Presented by DR. BENJAMIN GROSS.

Lupus Erythematosus, Clinically, vs. Lichen Planus, Histologically. Presented by CAPTAIN WILLIAM N. NEW (MC), USN.

Solar Dermatitis. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Solar Dermatitis Limited to the Left Elbow. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Lupus Erythematosus, Subacute, Patient Treated with Quinacrine (Atabrine) Hydrochloride. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. MILTON M. CAHN and DR. EDWIN J. LEVY.

Lupus Erythematosus, Chronic Discoid. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Psoriasis. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. I. HARDIN.

Lupus Erythematosus. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Albright's Syndrome. Presented by DR. NORMAN SCHNEEBERG (by invitation) and DR. BERTRAM SHAFFER.

Tinea Versicolor of Unusual Distribution. Presented by DR. HENRY HARRIS PERLMAN.

Cutaneous Blastomycosis. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. THOMAS S. KEMP, DR. MILTON M. CAHN, and DR. EDWIN J. LEVY.

Chronic Discoid Lupus Erythematosus of the Scalp. Presented by DR. STEPHEN WHELAN and (by invitation) DR. HARRY J. HURLEY.

Fox-Fordyce Disease vs. Lichen Simplex Chronicus. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. MILTON M. CAHN and DR. EDWIN J. LEVY.

Pityriasis Rubra Pilaris. Presented by DR. HENRY HARRIS PERLMAN.

Morphea. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. DOUGLASS A. DECKER, Allentown, Pa.

Calcification of the Skin. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Case for Diagnosis—Sarcoidosis? Presented by DR. BERTRAM SHAFFER and (by invitation) DR. MIRIAM REED.

Sarcoidosis, No Impromement with Cortisone. Presented by DR. BERTRAM SHAFFER and (by invitation) DR. EDWIN J. LEVY and DR. MILTON M. CAHN.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. H. E. TWINING and (by invitation) DR. MILTON M. CAHN and DR. EDWIN J. LEVY.

Congenital Preauricular Cyst. Presented by DR. LOUIS JAFFE.

Multiple Spider Nevi, Syndactylia, Dental Anomalies. Linear Nevus? (Linear Scleroderma? Csillag's Disease?). Presented by DR. LOUIS JAFFE.

Obituaries

JAMES KIRBY HOWLES, M.D.
1898-1953

James Kirby Howles passed away on April 2, 1953. With his passing, practitioners of medicine lost a stimulating example, a courageous spirit, a loyal and kindly friend. Few contemporaries possessed to an equal degree his capacity to influence the advancement of his special branch of medicine, dermatology and syphilology.

Dr. Howles was born in Memphis, Tenn., Jan. 5, 1898. After elementary schooling in Memphis, he served as a private in the United States Army in France during World War I. His medical education was begun unusually late since he was for several years connected with the hardwood lumber industry. He received his B.S., B.M., and M.D. degrees from the University of Cincinnati, and interned at Kansas City General Hospital. The degree of Medical Science (M.M.S.) was received from the University of Pennsylvania in 1932.

He was the second man to occupy the chair of dermatology and syphilology at Louisiana State University Medical School. Even more far-reaching in influence was his part in the establishment of a full-time residency at the Louisiana State Charity Hospital, the first of its kind in the deep South. His work in helping to revitalize the Louisiana Dermatological Society, in 1946, earned both him and Dr. M. T. Van Studdiford a certificate of merit from that organization in 1951.

In the course of an energetic professional career, he found time for the writing of a standard textbook on syphilis, in recognition of which the city of New Orleans presented him with an award of merit. His many other writings reflected varying interests in subjects within the scope of his specialty.

He was a member of the American College of Physicians and the American Academy of Dermatology and Syphilology.

At the time of his death, he was engaged in compiling material for a paper on chromoblastomycosis, to be presented in June of this year before the American Dermatological Association, in which distinguished society he had just been elected to membership.

Dr. Howles had one consuming hobby, the growing of prize camellias. Many of the visiting doctors and their wives will remember with pleasure his fine garden and the beautiful blossoms which he shared so generously.

He is survived by his wife, the former Mildred Dunn, and a son, James Thaddeus.

CHARLES BARRETT KENNEDY, M.D., New Orleans.

DR. JAMES KIRBY HOWLES

1898-1953

News and Comment

ANNOUNCEMENT

Hereafter the Directory of Dermatological Societies will be published once a year, in the July issue.

CORRECTION

In the article "Isophasic Reaction Following Experimental Superinfection of Leishmania Tropica," by Dr. A. Dostrovsky and his associates, published in the December 1952 issue, Leishman-Donovan bodies were incorrectly called Leishmania donovani in the footnotes of Tables 1 and 2, pages 667 and 668 respectively, and in line 6 on page 673.

The first paragraph of the summary, on page 675, should read as follows:

Successful superinfection of Leishmania tropica in patients with relapsing cutaneous leishmaniasis has been obtained. Eight out of 10 superinfections with 1,000,000 or 10,000,000 culture leptomonads of L. tropica in five patients with cutaneous leishmaniasis recidiva yielded positive leishmanial lesions. One million parasites induced such positive lesions following four out of five superinfections, and 10,000,000 induced them following four out of five superinfections. One superinfection, in a sixth patient, was unsuccessful.

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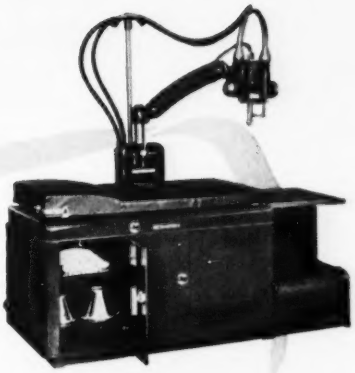

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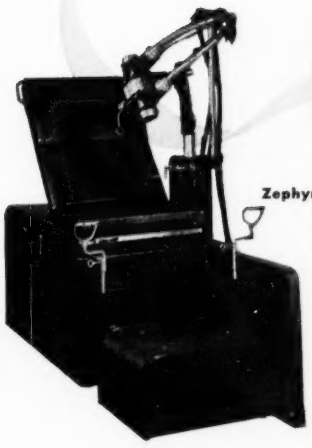

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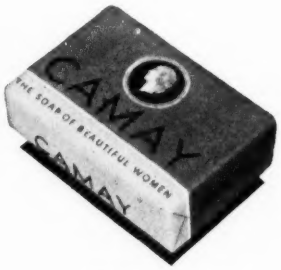

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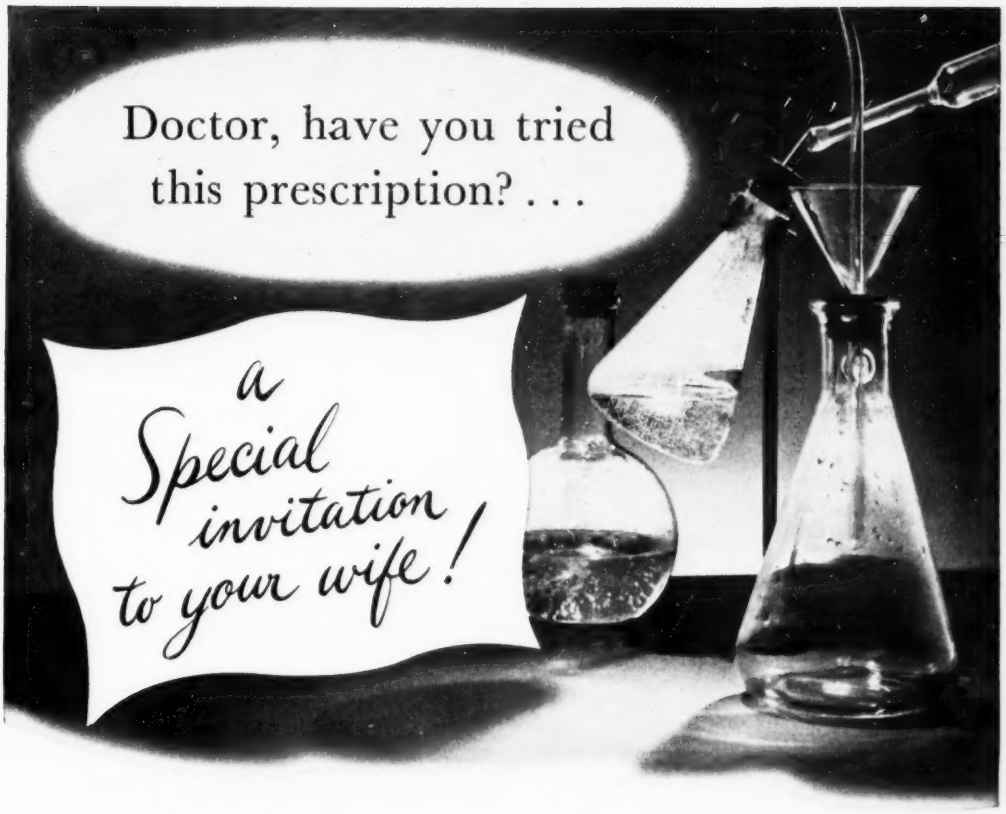

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*Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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1. New and Nonofficial Remedies, 1952.

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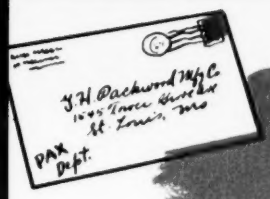

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1. *Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.* 2. *Slepyan, A. H. (1952), Ibid., 65:228, February.* 3. *Ruch, D. M. (1951), Communication to Abbott Laboratories.* 4. *Sauer, G. C. (1952), J. Missouri M. A. 49:911, November.*